

B23

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
26 April 2007 (26.04.2007)

PCT

(10) International Publication Number
WO 2007/045980 A1

(51) International Patent Classification:

A61K 31/41 (2006.01) A61P 29/00 (2006.01)
A61P 11/00 (2006.01) A61P 37/00 (2006.01)

(21) International Application Number:

PCT/IB2006/002931

(22) International Filing Date: 19 October 2006 (19.10.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

2793/DEL/2005 19 October 2005 (19.10.2005) IN

(71) Applicant (for all designated States except US): RANBAXY LABORATORIES LIMITED [IN/IN]; Plot No. 90, Sector - 32, Gurgaon 122001, Haryana (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): RAY, Abhijit [IN/IN]; Sector C-1, Flat No. 1408, Vasant Kunj, New Delhi 110070, Delhi (IN). DASTIDAR, Sunanda, G. [IN/IN]; B-138, Sarita Vihar, New Delhi 110044, Delhi (IN). SHIRUMALLA, Rajkumar [IN/IN]; 36A, Navyug Adarsh Apartments, Vikas Puri, New Delhi 110018, Delhi (IN). GUPTA, Suman [IN/IN]; House No. 954, Sector 31, Gurgaon 122001, Haryana (IN).

(74) Common Representative: RANBAXY LABORATORIES LIMITED; c/o DESHMUKH, JAY R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2007/045980 A1

(54) Title: COMPOSITIONS OF PHOSPHODIESTERASE TYPE IV INHIBITORS

(57) Abstract: Provided herein are pharmaceutical compositions comprising one or more phosphodiesterase inhibitors of type IV ("PDE-IV"), and at least one other active ingredients selected from muscarinic receptor antagonists (MRA), β_2 -agonists, p38 MAP Kinase inhibitors, and corticosteroids and optionally one or more pharmaceutically acceptable excipients and/or other therapeutic agents. In addition, methods of treating autoimmune, inflammatory or allergic diseases or disorders are provided.

WO 2007/045980

PCT/IB2006/002931

- 1 -

COMPOSITIONS OF PHOSPHODIESTERASE TYPE IV INHIBITORS

Field of the Invention

Provided herein are pharmaceutical compositions comprising one or more phosphodiesterase inhibitors of type IV ("PDE-IV"), and at least one other active
5 ingredient such as muscarinic receptor antagonists (MRA), β 2-agonists, p38 MAP Kinase inhibitors, or corticosteroids and optionally one or more pharmaceutically acceptable excipients. In addition, methods of treating autoimmune, inflammatory or allergic diseases or disorders are provided.

Background of the Invention

10 It is known that cyclic adenosine-3', 5'-monophosphate (cAMP) exhibits an important role of acting as an intracellular secondary messenger. The intracellular hydrolysis of cAMP to adenosine 5'-monophosphate (AMP) causes a number of inflammatory conditions, which include, but are not limited to, psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS),
15 eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, and ulcerative colitis. Cyclic nucleotide phosphodiesterases (PDE), a biochemically and functionally, highly variable superfamily of the enzyme, is the most important factor in the control of cAMP (as well as of cGMP) levels. Eight distinct families with more than 15 gene products are currently recognized. Although PDE I, PDE II, PDE III, PDE IV, and PDE VII all use
20 cAMP as a substrate, only the PDE IV and PDE VII types are highly selective for hydrolysis of cAMP. Accordingly, inhibitors of PDE, particularly the PDE IV inhibitors, such as rolipram or Ro-1724, are known as cAMP-enhancers. Immune cells contain PDE IV and PDE III, of which PDE IV is prevalent in human mononuclear cells. Thus, the inhibition of phosphodiesterase type IV has been a target for modulation and, accordingly,
25 for therapeutic intervention in a range of disease processes. The initial observation that xanthine derivatives, theophylline and caffeine inhibit the hydrolysis of cAMP led to the discovery of the required hydrolytic activity in the cyclic nucleotide phosphodiesterase (PDE) enzymes. More recently, distinct classes of PDE have been recognized, and their selective inhibition has led to improved drug therapy. Thus, it was recognized that
30 inhibition of PDE IV could lead to inhibition of inflammatory mediator release and airway smooth muscle relaxation.

PCT/TB2006/002931

- 2 -

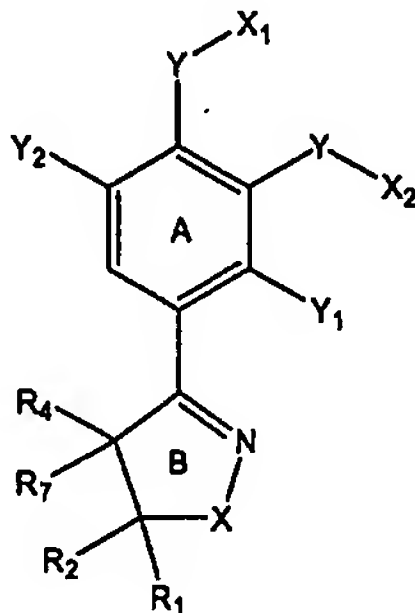
Particular 3-aryl-2-isoxazoline compounds are known as anti-inflammatory agents and particular isoxazoline compounds are known as inhibitors of TNF release. However, there remains a need for new selective inhibitors of phosphodiesterase (PDE) type IV, as well as compositions thereof in combination with one or more other therapeutic agents.

5 Summary of the Invention

In one aspect, provided are pharmaceutical compositions comprising one or more phosphodiesterase inhibitors of type IV ("PDE-IV"), and at least one other active ingredient such as muscarinic receptor antagonists (MRA), β 2-agonists, p38 MAP Kinase inhibitors, or corticosteroids and optionally one or more pharmaceutically acceptable excipients, wherein the PDE-IV is one or more compounds having the structure of Formula Ia or Formula Ib,

wherein:

a. Formula Ia is:



15

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides, wherein

When X is oxygen,

20 **R₁** can be hydrogen, alkyl, heterocyclyl, $-(CH_2)_mC(=O)R_3$, or $(CH_2)_{1-4}OR'$, (wherein m is an integer 0-2, R₃ can be alkyl, cycloalkyl, heterocyclyl, or optionally substituted R_p or R_q, wherein R_p can be heterocyclyl or heteroaryl ring, wherein the rings are attached to $(CH_2)_mC(=O)$ through N, and R_q can be heterocyclyl or heteroaryl ring wherein the rings are attached to $-(CH_2)_mC(=O)$ through C, and

WO 2007/045980

PCT/IB2006/002931

- 3 -

wherein R' can be can be alkyl, alkenyl, alkynyl, saturated or unsaturated cycloalkyl, aryl, heterocyclyl or heteroaryl);

- R₂** can be (CH₂)_mC(=O)R₃, -(CH₂)₁₋₄OR', or C(=O)NR_xR_y {where m, R₃ and R' are as defined above, and wherein R_x and R_y each independently can be hydrogen, alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, cycloalkyl, carboxy, -S(O)_mR₅ (wherein R₅ can be hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl), aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl}, or R₁ and R₂ together form an optionally substituted cycloalkyl or heterocyclyl ring wherein the optional substituent is oxo, alkyl, alkenyl, alkynyl, halogen, nitro, -NH₂, -NHC(=O)OR₆, -C(=O)NR_xR_y, cyano, hydroxy, alkoxy, or substituted amino (wherein R₆ can be alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclylalkyl), with the proviso that if R₁ is -(CH₂)₁₋₄OR', then R₂ is also -(CH₂)₁₋₄OR', and with the proviso that if R₁ is C(=O)NR_xR_y, then R₂ is also C(=O)NR_xR_y;
- R₄** can be hydrogen; alkyl; -OR₅; halogen; -NH₂, substituted amino; cyano; carboxy; or -C(=O)NR_xR_y (wherein R₅, R_x and R_y are as defined above); or R₂ and R₄ forms an optionally substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s) selected from the group consisting of N, O and S, wherein the substituents can be one or more of alkyl, halogen, hydroxy, alkoxy, -NH₂ or substituted amino (wherein R₃ and R_x and R_y are as defined above), with the proviso that R₂ and R₄ together does not form -CH₂-O-CH₂-O-CH₂-;
- R₇** can be hydrogen, alkyl, alkenyl, alkynyl, -OR₅, halogen, cyano, -NH₂, or substituted amino;
- X₁** and **X₂** each independently can be hydrogen, alkyl, alkaryl, cycloalkyl, alkaryl, alkenyl, cycloalkylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, -(CH₂)_gC(=O)NR_xR_y, -(CH₂)_{g1}C(=O)OR₃ or heteroarylalkyl; wherein g₁ can be an integer from 1-3 (wherein R_x, R_y, g and R₃ are as defined above);

WO 2007/045980

PCT/IB2006/002931

- 4 -

Y can each independently be an oxygen atom; a sulphur atom; or -NR (wherein R can be hydrogen, acyl, aryl, or alkyl);

Y₁ and **Y₂** each independently can be hydrogen; alkyl; -OR; -SR; or -NHR (wherein R is as defined above);

5 wherein any of **Y₁** and **X₂** & **X₁** and **Y₂** together optionally form a ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms such as N, O and S, and **X₁** and **X₂** can together optionally form a ring fused with ring A, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms such as N, O or S, and

10

When X is NR₇, or S (wherein R₇ can be hydrogen, or C₁₋₆ alkyl)

R₁ and **R₂** can each independently be alkyl, alkenyl, alkynyl, alkoxy, hydroxy, cyano, nitro, halogen, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, NH₂, substituted amino, carboxy, -(CH₂)_mC(=O)R₃, -C(=O)NR_xR_y, or (CH₂)₁₋₄OR',
 15 {wherein m is an integer 0-2, R₃ can be alkyl, cycloalkyl, heterocyclyl, or optionally substituted R_p or R_q (wherein R_p can be heterocyclyl or heteroaryl ring, wherein the rings are attached to (CH₂)_mC(=O) through N, and R_q can be heterocyclyl or heteroaryl ring wherein the rings are attached to -(CH₂)_mC(=O) through C), wherein R' can be can be alkyl, alkenyl, alkynyl, saturated or
 20 unsaturated cycloalkyl, aryl, heterocyclyl or heteroaryl, and wherein R_x and R_y each independently can be hydrogen, alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, cycloalkyl, carboxy, -S(O)_mR₅ (wherein R₅ can be hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl), aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, or
 25 heterocyclylalkyl}, or **R₁** and **R₂** together can form an optionally substituted cycloalkyl or heterocyclyl ring wherein the optional substituent is oxo, alkyl, alkenyl, alkynyl, halogen, nitro, -NH₂, -NHC(=O)OR₆ (wherein R₆ can be alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclylalkyl), -C(=O)NR_xR_y, cyano, hydroxy, alkoxy, or substituted amino;

30 **R₄** can be hydrogen; alkyl; -OR₅; halogen; -NH₂, substituted amino; cyano; carboxy; or -C(=O)NR_xR_y (wherein R₅, R_x and R_y are as defined above); or **R₂** and **R₄** forms

WO 2007/045980

PCT/IB2006/002931

- 5 -

an optionally substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s) selected from the group consisting of N, O and S, wherein the substituents can be one or more of alkyl, halogen, hydroxy, alkoxy or substituted amino (wherein R_3 and R_x and R_y are as defined above), with the proviso that R_2 and R_4 together does not form -CH₂-O-CH₂-O-CH₂-;

R_7 can be hydrogen, alkyl, alkenyl, alkynyl, -OR₅, halogen, cyano, -NH₂, or substituted amino;

X_1 and X_2 each independently can be alkyl, cycloalkyl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclalkyl;

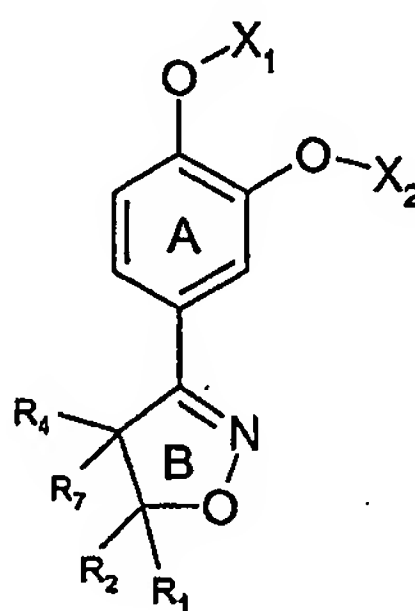
Y can each independently be an oxygen atom; a sulphur atom; or -NR (wherein R can be can be hydrogen, acyl, aryl, or alkyl);

Y_1 and Y_2 each independently can be hydrogen, alkyl, -OR, -SR, or -NHR (wherein R is as defined above);

wherein any of Y_1 and X_2 & X_1 and Y_2 together optionally form a ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms such as N, O and S;

X_1 and X_2 can together optionally forms a cyclic ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms such as N, O or S.

b. Formula Ib is:



Formula Ib

WO 2007/045980

PCT/IB2006/002931

- 6 -

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides, wherein

R_1 and R_2 together forms an optionally substituted cycloalkyl or heterocyclyl ring wherein one or more optional substituent are oxo, alkyl, alkaryl, alkenyl, alkynes, heterocyclylalkyl, cycloalkylalkyl, $-SO_2NR_xR_y$, halogen, $-NH_2$, $-(CH_2)_gC(=O)NR_xR_y$, -
5 $NHC(=O)OR_6$, $-NHC(=O)NR_xR_y$, $-C(=O)OR_3$, $-NHC(=O)R_x$, $-SO_2R_3$, cyano, hydroxy, alkoxy, substituted amino, or $-C(=O)R_3$ (wherein R_xR_y g, R_6 and R_3 are as defined above);

R_4 can be hydrogen; alkyl, hydroxyl, halogen, or carboxy;

R_7 can be hydrogen, or alkyl;

10 R_1 can be independently hydrogen or alkyl and R_2 and R_4 forms an optionally substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s) selected from the group consisting of N, O and S, wherein the substituents is one or more of oxo, alkyl, $-C(=O)OR_3$, $-SO_2R_3$, halogen, hydroxy, alkoxy, $-NH_2$ or substituted amino (wherein R_3 is as defined below), with the
15 proviso that R_2 and R_4 together does not form $-CH_2-O-CH_2-O-CH_2-$;

X_1 and X_2 can be hydrogen, alkyl, cycloalkyl, alkaryl, alkenyl, cycloalkylalkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $-(CH_2)_gC(=O)NR_xR_y$ or $-(CH_2)_{g_1}C(=O)OR_3$ (wherein g can be an integer from 0-3 and g_1 can be an integer from 1-3, and R_x , R_y and R_3 are as defined below);

20 X_1 and X_2 together can optionally form a cyclic ring fused with the ring A shown in Formula I, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms N, O or S;

wherein R_3 can be alkyl, cycloalkyl or heterocyclyl;

wherein the halogen can be F, Cl, Br, or I; R_x and R_y each independently can be
25 hydrogen, alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, carboxy, cycloalkyl, $-S(O)_mR_5$, aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclylalkyl; m can be an integer between 0-2; R_6 can be alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclylalkyl;

wherein R_5 can be hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl,
30 heteroarylalkyl, heterocyclyl or heterocyclylalkyl;

WO 2007/045980

PCT/IB2006/002931

- 7 -

In another aspect, provided are pharmaceutical compositions comprising one or more phosphodiesterase inhibitors of type IV ("PDE-IV"), and at least one other active ingredient such as muscarinic receptor antagonists (MRA), β 2-agonists, p38 MAP Kinase inhibitors, and corticosteroids and one or more pharmaceutically acceptable excipients, wherein the PDE-IV is one or more compounds having the structure of Formula Ia and Formula Ib, as described herein.

The pharmaceutical compositions of each of the above aspects can include one or more of the following embodiments. For example, the one or more compounds of Formula Ia and Formula Ib may be:

- 10 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-en-6-ol (Compound No. 1),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-*N*-(4-fluorophenyl)-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-carboxamide (Compound No. 2),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-7-(tetrahydrofuran-3-ylcarbonyl)-1-oxa-2,7-diazaspiro[4.4]non-2-ene (Compound No. 3),
- 15 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-*N,N*-dimethyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-sulfonamide (Compound No. 4),
- N*-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-carboxamide (Compound No. 5),
- 20 2-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-en-7-yl}acetamide (Compound No. 6),
- Hydrochloride salt of 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-8-prolyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 7),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-(2-morpholin-4-yl-ethyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 8),
- 25 *N*-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxamide (Compound No. 9),
- 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-8-(methylsulfonyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 10),

WO 2007/045980

PCT/IB2006/002931

- 8 -

- 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.4]non-2-ene (Compound No. 11),
- 3-[3,4-bis(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 12),
- 5 3-(3,4-diisopropoxyphenyl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 13),
3-[3-methoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 14),
3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-en-8-one (Compound No. 15),
- 10 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-en-8-ol (Compound No. 16).
3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-7-isopropyl-1-oxa-2, 7-diazaspiro [4.4] non-2-ene (Compound No. 17),
3-[3-(cyclopentyloxy)-4-methoxyphenyl]-7-(cyclopropylcarbonyl)-1-oxa-2,7-
15 diazaspiro[4.4]non-2-ene (Compound No. 18),
N-benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-carboxamide (Compound No. 19),
7-acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene (Compound No. 20),
- 20 *Tert*-butyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene-7-carboxylate (Compound No. 21),
N-butyl-*N*'-{3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}urea (Compound No. 22),
N'-{3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}-*N*'-(2-
25 methoxyphenyl)urea (Compound No. 23),
3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-ol (Compound No. 24),
Hydrochloride salt of 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene (Compound No. 25),

WO 2007/045980

PCT/IB2006/002931

- 9 -

- 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-one
(Compound No. 26),
- 3-[3,4-bis(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 27),
- 5 3-[3,4-Bis(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 28),
- 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-en-4-ol
(Compound No. 29),
- (R)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
10 (Compound No. 30),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-(cyclopropylmethyl)-1-oxa-2,8-
diazaspiro[4.5]dec-2-ene (Compound No. 31),
- N*-Benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-
carboxamide (Compound No. 32),
- 15 3-[3,4-Bis(benzyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 33),
- 4-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)benzene-1,2-diol (Compound No. 34),
- 7-Amino-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-en-6-
one (Compound No. 35),
- Ethyl 8-benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-
20 ene-4-carboxylate (Compound No. 36),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-ene-4-carboxylic
acid (Compound No. 37),
- 8-Benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene
(Compound No. 38),
- 25 Ethyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-ene-4-
carboxylate (Compound No. 39),
- 3-[3-(Difluoromethoxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 40),

WO 2007/045980

PCT/IB2006/002931

- 10 -

- 2-(Difluoromethoxy)-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)phenol (Compound No. 41)
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-en-6-one (Compound No. 42).
- 5 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,6a-dimethyl-3a*H*-cyclopenta[*d*]isoxazole-4,6(5*H*,6a*H*)-dione (Compound No. 43),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazole (Compound No. 44).
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one
10 (Compound No. 45),
- Tert*-butyl [(3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl)amino]carbonyl]carbamate (Compound No. 46),
- N*-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}cyclopentanecarboxamide (Compound No. 47),
- 15 8-Acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 48),
- 8-(Cyclopentylcarbonyl)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 49),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-(2-piperidin-1-ylethyl)-1-oxa-2,8-
20 diazaspiro[4.5]dec-2-ene (Compound No. 50),
- 3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 51),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1,8-dioxa-2-azaspiro[4.5]dec-2-ene (Compound No. 52),
- 25 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a*H*-cyclopenta[*d*]isoxazole-4,6(5*H*,6a*H*)-dione (Compound No. 53),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-ethyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 54),

WO 2007/045980

PCT/IB2006/002931

- 11 -

- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-vinyl-1-oxa-2-azaspiro[4.5]dec-2-en-8-ol
(Compound No. 55),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazole
(Compound No. 56),
- 5 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole
(Compound No. 57),
- N*-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}methanesulfonamide(Compound No. 58),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-methyl-1-oxa-2-azaspiro[4.5]dec-2-en-8-ol
10 (Compound No. 59),
- 3-[3-(Allyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 60),
- 3-[3-(2-Chloroethoxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 61),
- 15 2-(Cyclopentyloxy)-4-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenol (Compound No. 62),
- 3-(4-Butoxy-3-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 63),
- 3-(3-Isobutoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 64),
20
- 3-[3-Butoxy-4-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 65),
- 3-(3-Butoxy-4-ethoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 66),
- 3-[3-Butoxy-4-(cyclohexyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
25 No. 67),
- 3-[3-(Cyclohexylmethoxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 68),
- 3-[3-(Cyclohexylmethoxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 69),

WO 2007/045980

PCT/IB2006/002931

- 12 -

3-[4-Butoxy-3-(cyclohexylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 70),

3-(4-Isobutoxy-3-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No.
71),

5 3-(4-Butoxy-3-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No.
72),

3-[4-(Cyclohexylmethoxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 73),

3-[3-Isopropoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
10 (Compound No. 74),

3-[3-(Cyclopropylmethoxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 75),

3-[3-(Cyclopropylmethoxy)-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-
azaspiro[4.4]non-2-ene (Compound No. 76),

15 3-[4-Butoxy-3-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 77),

3-[3-(Cyclopropylmethoxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 78),

3-(3-Isobutoxy-4-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No.
20 79),

3-[4-(Cyclopropylmethoxy)-3-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 80),

3-[4-(cyclohexyloxy)-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 81)

25 3-[4-(Cyclohexylmethoxy)-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
ene (Compound No. 82),

3-[4-(Cyclopropylmethoxy)-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
ene (Compound No. 83),

WO 2007/045980

PCT/IB2006/002931

- 13 -

3-[3-(Cyclopentyloxy)-4-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 84),

3-[3-(Cyclopentyloxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 85),

5 3-[3-(Cyclopropylmethoxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 86),

3-[4-(Cyclopentyloxy)-3-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 87),

3-[3-Isopropoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
10 (Compound No. 88),

3-(4-Ethoxy-3-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 89),

3-[3-(Cyclopentyloxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 90),

15 3-[4-Butoxy-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 91),

3-[3-(Cyclopentyloxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 92),

3-[3-(Cyclopentyloxy)-4-(cycloheptyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
20 (Compound No. 93),

3-[3-(Cyclopentyloxy)-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-
2-ene (Compound No. 94),

3-[4-(Cyclohexylmethoxy)-3-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 95),

25 3-[4-(Cyclohexylmethoxy)-3-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-
2-ene (Compound No. 96),

3-[3-(Cyclopropylmethoxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 97),

WO 2007/045980

PCT/IB2006/002931

- 14 -

- 3-[4-(Cyclopentyloxy)-3-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 98),
- 3-[4-(Cyclopropylmethoxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 99),
- 5 3-[4-(Cyclopentyloxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 100),
- 3-(3-Isopropoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 101),
- 3-(4-Ethoxy-3-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
10 No. 102),
- 3-[3-Butoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 103),
- 3-[3-Butoxy-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 104),
- 15 3-(3-Butoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 105),
- 3-(3-Butoxy-4-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 106),
- 3-[3-(Cyclohexylmethoxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
20 (Compound No. 107),
- 3-[3-(Cyclohexylmethoxy)-4-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 108),
- 3-[3-(Cyclohexylmethoxy)-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 109),
- 25 3-[3-(Cyclohexylmethoxy)-4-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 110),
- 3-[4-(Cyclohexylmethoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 111),

WO 2007/045980

PCT/IB2006/002931

- 15 -

3-[4-(Cyclopropylmethoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 112),

3-[4-(Cyclopentyloxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 113),

5 3-[4-(3-Isobutoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 114),

3-[3-(Cycloheptyloxy)-4-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
ene (Compound No. 115),

10 3-[3-(Cycloheptyloxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 116),

3-[4-Butoxy-3-(cycloheptyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 117),

3-[3-(Cycloheptyloxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 118),

15 3-[3-(Cycloheptyloxy)-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 119),

3-(3-Ethoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 120),

3-[4-(Cycloheptyloxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 121),

20 3-[4-(Cyclopropylmethoxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 122),

3-[4-(Cyclohexylmethoxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 123),

25 (S)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 124),

3-(3-Butoxy-4-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 125),

3-(3-Ethoxy-4-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 126),

WO 2007/045980

PCT/IB2006/002931

- 16 -

- 3-[4-(Cyclopentyloxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 127),
- 3-(4-Butoxy-3-ethoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 128),
- 3-(3-Ethoxy-4-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 129),
- 3-[3-(Cycloheptyloxy)-4-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 130),
- 3-[3-(Cycloheptyloxy)-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 131),
- 3-[3-(Cycloheptyloxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 132),
- 3-(4-Butoxy-3-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 133),
- 3-(4-Ethoxy-3-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 134),
- 3-[4-(Morpholin-4-ylethoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 135),
- 3-(4-Isopropoxy-3-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 136),
- 2-[5-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]cyclopentanol (Compound No. 137),
- N*-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}-2-fluorobenzamide (Compound No. 138),
- N*-{3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}benzamide (Compound No. 139).
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]isoxazole (Compound No. 140)
- 7-(Cyclopentylcarbonyl)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene (Compound No. 141),

WO 2007/045980

PCT/IB2006/002931

- 17 -

Tert-butyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-3a,4,6,6a-tetrahydro-5*H*-pyrrolo[3,4-*d*]isoxazole-5-carboxylate (Compound No. 142),

3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxamide (Compound No. 143),

5 *N*-Butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene-7-carboxamide (Compound No. 144).

3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-7-(methylsulfonyl)-1-oxa-2,7-diazaspiro[4.5]dec-2-ene (Compound No. 145),

3-[4-Methoxy-3-(pyridin-3-ylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
10 (Compound No. 146),

5-Acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]isoxazole (Compound No. 147),

3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-(methylsulfonyl)-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]isoxazole (Compound No. 148),

15 4-Bromo-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 149),

3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,5,6,7a-tetrahydro-1,2-benzisoxazol-7(4*H*)-one (Compound No. 150).

3-[4-(Difluoromethoxy)-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxo-2-
20 azaspiro[4.4]non-2-ene (Compound No. 151),

3-[4-(Cyclopentyloxy)-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 152),

3-[4-Butoxy-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 153),

25 3-(3-{{3-(Benzyloxy)cyclopentyl}oxy}-4-methoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 154),

7-Acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene (Compound No. 155),

WO 2007/045980

PCT/IB2006/002931

- 18 -

- 3-[4-Methoxy-3-(pyridin-2-ylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 156),
- 3-[3-(2,3-Dihydro-1*H*-inden-2-ylloxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 157),
- 5 3-[3-(2,3-Dihydro-1*H*-inden-2-ylloxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 158),
- 3-[4-(Cyclopropylmethoxy)-3-(2,3-dihydro-1*H*-inden-2-ylloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 159),
- 3-[3-(2,3-Dihydro-1*H*-inden-2-ylloxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-
10 2-ene (Compound No. 160),
- 2-(2,3-Dihydro-1*H*-inden-2-ylloxy)-4-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenol
(Compound No. 161),
- N*-cyclopropyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetamide (Compound No. 162),
- 15 Hydrochloride salt of 3-[4-methoxy-3-(piperidin-3-ylloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 163),
- 2-[5-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetamide
(Compound No. 164),
- Ethyl [5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetate (Compound
20 No. 165),
- [5-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetonitrile (Compound
No. 166),
- 3-{3-[(2,6-Dichloropyridin-4-yl)methoxy]-4-methoxyphenyl}-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 167),
- 25 [3-(3-Cyclopentylloxy-4-methoxy phenyl)-5-(4-carboxylic acid tert butylester-piperazin-1-yl-carbonyl)-4,5-dihydroisoxazol-5-yl]-({4-carboxylic-acid- tert butyl ester piperazine-1-yl) ethanone (Compound No. 168),

WO 2007/045980

PCT/IB2006/002931

- 19 -

1-{1-[5-(4-Acetyl-4-phenyl-piperidine-1-carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazole-5-yl]-4-acetyl-4-phenyl-piperidin-4-yl}-ethanone
(Compound No. 169)

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-
5 isoxazol-5-yl]-pyrrolidin-1-yl-ethanone (Compound No. 170),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(piperidine-1-carbonyl)-4,5-dihydro-isoxazol-
5-yl]-piperidin-1-yl-ethanone (Compound No. 171),

3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(pyrrolidin-2-carboxylic acid methyl ester-1-
carbonyl)-4,5-dihydro-isoxazol-5-yl)-[{pyrrolidine-2-carboxylic acid methyl ester-5-yl}]
10 ethanone (Compound No. 172),

[5-[4-(4-Chlorophenyl)-4-hydroxy-piperidine-1-carbonyl]-3-(3-cyclopentyloxy-4-
methoxy-phenyl)-4,5-dihydro-isoxazol-5-yl]-[4-(4-chlorophenyl)-4-hydroxy-piperidin-1-
yl]-ethanone (Compound No. 173)

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(hydroxymethyl-piperidine-1-carbonyl)-4,5-
15 dihydro-isoxazol-5-yl]-(4-hydroxymethyl-piperidin-1-yl)-ethanone (Compound No. 174),

[5-(5-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-(carbonyl)-3-(3-cyclopentyloxy-4-
methoxy-phenyl)-4,5-dihydro-isoxazol-5-yl]-5-benzyl-2,5-diazabicyclo-[2.2.1]hept-2-yl-
ethanone (Compound No. 175),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperidin-
20 1-yl-methanone (Compound No. 176),

4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-
piperazine-1-carboxylic acid tert-butyl ester (Compound No. 177),

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-carbonyl]-
pyrrolidin-2-carboxylic acid (Compound No. 178),

25 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-carbonyl]-
pyrrolidine-2-carboxylic acid methyl ester (Compound No. 179),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-yl]-
pyrrolidin-1-yl-methanone (Compound No. 180),

WO 2007/045980

PCT/IB2006/002931

- 20 -

- [1-4]-Bipiperidinyl-1-yl-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 181),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-4-phenyl-piperidine-4-yl}-ethanone (Compound No. 182),
- 5 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-methyl-piperazin-1-yl)-methanone (Compound No. 183),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperazin-1-yl-methanone (Compound No. 184),
- [4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-methanone (Compound No. 185),
- 10 {4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-[1,4]diazepan-1-yl}-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 186),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-cyclopropylmethyl-piperazin-1-yl)-methanone (Compound No. 187),
- 15 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-isobutyl-1-piperazin-1-yl)-methanone (Compound No. 188),
- [3-Hydroxymethyl-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 189),
- 20 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-hydroxy-piperidin-1-yl)-methanone (Compound No. 190),
- (4-Benzyl-piperidin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 191),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-piperidin-4-one (Compound No. 192),
- 25 [4-(4-Bromophenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 193),
- (5-Benzyl-2,5-diaza-bicyclo [2.2.1] hept-2-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 194),

WO 2007/045980

PCT/IB2006/002931

- 21 -

- (4-Benzyl-piperazin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4, 5-dihydro-isoxazol-5-yl]-methanone (Compound No. 195),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4, 5-dihydro-isoxazole-5-carbonyl]-pyrrolidin-2-carboxylic acid methyl amide (Compound No. 196),
- 5 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-pyrrolidine-2-carboxylic acid diethyl amide (Compound No. 197),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(2-hydroxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 198),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonyl]-
- 10 piperidine-2-carboxylic acid methyl ester (Compound No. 199),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carboxyl]-pyrrolidine-2-carboxylic acid amide (Compound No. 200),
- 3-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-bicyclo[2.2.1]heptan-2-one (Compound No. 201),
- 15 3-[3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxa-2-aza-spiro[4.4]non-2-en-6-one (Compound No. 202),
- 3-[3-Cyclopentyloxy-4-methoxy-phenyl)-7-methyl-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-6,9-dione (Compound No. 203),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(2-methoxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 204),
- 20 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxa-2-aza-spiro [4.4] non-2-ene (Compound No. 205),
- 3-(3-Cyclopropylmethoxy-4-methoxy-phenyl)-1,7-dioxa-2-aza-spiro[4.4]non-2-ene (Compound No. 206),
- 25 3-(4-Difluoromethoxy-3-propoxy-phenyl)-1,7-dioxa-2-aza-spiro[4.4]non-2-ene (Compound No. 207),
- 3-(4-Difluoro-3-butoxy-phenyl)-1,7-dioxa-2-aza-spiro[4.4]non-2-ene (Compound No. 208),

WO 2007/045980

PCT/IB2006/002931

- 22 -

3-(4-Difluoromethoxy-3-isobutoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
(Compound No. 209),

3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 210),

5 3-(3-Benzoyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
(Compound No. 211),

3-(4-Difluoromethoxy-3-cyclopentylloxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 212);

3-(3,4-Bis-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
10 No. 213),

3-(3-Butoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro [4,4] non-2-ene
(Compound No. 214),

3-[3-(Bicyclo[2.2.1]hept-2-ylloxy)-4-difluoromethoxy-phenyl]-1,7-dioxo-2-aza-
spiro[4.4]non-2-ene (Compound No. 215),

15 3-(4-Difluoromethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 216),

3-(4-Benzoyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 217),

3-(3-Cycloheptyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
20 (Compound No. 218),

4-(1,7-Dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 219),

3-[3-(indan-2-ylloxy)-4-methoxy-phenyl]-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
(Compound No. 220),

3-(4-Ethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
25 No. 221),

3-(3-Methoxy-4-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No.
222),

3-(4-Isopropoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 223),

WO 2007/045980

PCT/IB2006/002931

- 23 -

- 3-(4-Butoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 224),
- 3-(4-Cyclopentyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene (Compound No. 225),
- 5 3-(4-(Isobutoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 226),
- 3-(4-Cyclohexyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene (Compound No. 227),
- 3-(4-Cyclopropylmethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 228),
- 10 3-(3,4-Dimethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 229),
- 3-(3-Ethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 230),
- 3-(4-Methoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
- 15 No. 231),
- 3-(3-Isopropoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 232),
- 3-(3-Butoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 233),
- 20 3-(3-Isobutoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 234),
- 3-[4-Methoxy-3-(3-methyl-butoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 235),
- 3-(3-Cyclohexyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene (Compound No. 236),
- 25 3-(3-Cycloheptyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene (Compound No. 237),
- 3-[4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 238),

WO 2007/045980

PCT/IB2006/002931

- 24 -

- 3-(3-Benzoyloxy-4-methoxy-phenyl)-1,7-dioxa-2-aza-spiro[4.4]non-2-ene (Compound No. 239),
- 5-(1,7-Dioxa-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 240),
- 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-
5 carboxylic acid isopropyl ester (Compound No. 241),
- Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene (Compound No. 242),
- 4-Chloro-N-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carbonyl]-benzene sulfonamide (Compound No. 243),
- 10 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2, 8-diaza-spiro [4.5] dec-2-ene-8-carboxylic acid-(2,6-difluoro-phenyl)-amide (Compound No. 244),
- 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-carboxylic acid-(2,4-dichloro-phenyl)-amide (Compound No. 245),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-carbamic
15 acid isopropyl ester (Compound No. 246),
- Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-ylamine (Compound No. 247),
- 2-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-isoindole-1,3-dione (Compound No. 248),
- 20 7-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-oxa-6-aza-spiro[3.4]oct-6-ene (Compound No. 249),
- 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-ene (Compound No. 250),
- 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-7-
25 carboxylic acid tert-butyl ester (Compound No. 251),
- Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene (Compound No. 252),
- 3-[3-[(3*S*)-1-Benzylpyrrolidin-3-yl]oxy]-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 253),

WO 2007/045980

PCT/IB2006/002931

- 25 -

- 3-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]propan-1-ol
(Compound No. 254),
- [2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetonitrile
(Compound No. 255),
- 5 4-[(5S or 5R)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound
No. 256),
- 4-[(5R or 5S)-1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound
No. 257),
- 5-[(5S or 5R)-1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound
10 No. 258),
- (5S or 5R)-3-(3,4-Dimethoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 259),
- (5R or 5S)-3-(3,4-Dimethoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 260),
- 15 2-(Benzyloxy)-4-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenol (Compound No. 261),
- 2-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]ethanol
(Compound No. 262),
- 3-[4-(Difluoromethoxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 263),
- 20 3-[3-(Cyclohexyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 264),
- (5R or 5S)-3-[4-(Difluoromethoxy)-3-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
ene (Compound No. 265),
- (5S or 5R)-3-[4-(Difluoromethoxy)-3-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
25 ene (Compound No. 266),
- Ethyl [2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetate
(Compound No. 267),

WO 2007/045980

PCT/IB2006/002931

- 26 -

- 3-[4-(Difluoromethoxy)-3-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 268),
- 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl cyclohexanecarboxylate (Compound No. 269),
- 5 5-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]pentanoic acid (Compound No. 270),
- 3-[3-(2,2,2-Trifluoroethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 271),
- 3-[3-(Cyclopentylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 272),
- 10 *N*-cyclopropyl-2-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetamide (Compound No. 273),
- 2-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetamide (Compound No. 274),
- 15 2-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]-*N*-methylacetamide (Compound No. 275),
- 3-[3-(Cyclopentylloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 276),
- 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl
- 20 cyclopropanecarboxylate (Compound No. 277),
- 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl morpholine-4-carboxylate (Compound No. 278),
- 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl benzoate (Compound No. 279),
- 25 5-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy] pentanamide (Compound No. 280),
- 3-[3-Propoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 281,

WO 2007/045980

PCT/IB2006/002931

- 27 -

- 3-[3-Isopropoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 282),
- 3-[3-(Cyclopropylmethoxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-
azaspiro[4.4]non-2-ene (Compound No. 283),
- 5 3-[3-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-
azaspiro[4.4]non-2-ene (Compound No. 284),
- 5-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)phenol (Compound
No. 285),
- 3-[3-Methoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
10 (Compound No. 286),
- 3-[3-Ethoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 287),
- 3-[3-Butoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
ene10019955 (Compound No. 288),
- 15 3-[3-(Cyclohexylmethoxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-
azaspiro[4.4]non-2-ene (Compound No. 289),
- 3-{{2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy}methyl}
benzonitrile (Compound No. 290),
- 2-{{2-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]ethyl}-
20 1*H*-isoindole-1,3(2*H*)-dione (Compound No. 291),
- 3-[3-(Cyclohexyloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
ene (Compound No. 292),
- Ethyl [5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)
phenoxy]acetate (Compound No. 293),
- 25 3-[3-(Cyclohexylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
ene (Compound No. 294),
- Tert*-butyl [2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-
yl)phenoxy]acetate (Compound No. 295),

WO 2007/045980

PCT/IB2006/002931

- 28 -

N-cyclopropyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)phenoxy]acetamide (Compound No. 296),

2-(Cyclopentyloxy)-4-[(5R or 5S)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol (Compound No. 297),

5 2-(Cyclopentyloxy)-4-[(5S or 5R)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol (Compound No. 298),

N-benzyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)phenoxy]acetamide (Compound No. 299),

10 N-Cyclopentyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)phenoxy]acetamide (Compound No. 300),

Tert-butyl 4-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]piperidine-1-carboxylate (Compound No. 301),

15 Hydrochloride salt of 3-[4-(difluoromethoxy)-3-(piperidin-4-yloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 302),

3-{3-[(1-Acetylpiperidin-4-yl)oxy]-4-(difluoromethoxy)phenyl}-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 303),

Tert-butyl (3S)-3-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]pyrrolidine-1-carboxylate (Compound No. 304),

20 Tert-butyl (3R)-3-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]pyrrolidine-1-carboxylate (Compound No. 305),

Tert-butyl 3-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]piperidine-1-carboxylate (Compound No. 306),

25 Tert-butyl (2S)-2-[[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]methyl]pyrrolidine-1-carboxylate (Compound No. 307),

(5R or 5S)-3-[3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 308),

(5S or 5R)-3-(3-isopropoxy-4-methoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 309),

WO 2007/045980

PCT/IB2006/002931

- 29 -

(5S or 5R)-3-[3-(Cyclopropylmethoxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 310),

2-(Cyclopropylmethoxy)-4-[(5S or 5R)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol (Compound No. 311),

5 4-[(5S or 5R)-1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl]-2-isopropoxyphenol (Compound No. 312),

(5S or 5R)-3-[3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 313),

10 (5S or 5R)-3-[3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 314),

(5S or 5R)-3-[4-(difluoromethoxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 315),

15 (5R or 5S)-3-[4-(difluoromethoxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 316),

2-(Cyclopropylmethoxy)-4-[(5R or 5S)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol (Compound No. 317),

4-[(5R or 5S)-1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl]-2-isopropoxyphenol (Compound No. 318),

20 (5R or 5S)-3-[3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 319),

(5R or 5S)-3-[4-(difluoromethoxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 320),

25 Hydrochloride salt of 3-{4-(difluoromethoxy)-3-[(3S)-pyrrolidin-3-yloxy]phenyl}-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 321),

Hydrochloride salt of 3-{4-(difluoromethoxy)-3-[(2S)-pyrrolidin-2-ylmethoxy]phenyl}-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 322),

Hydrochloride salt of 3-{4-(difluoromethoxy)-3-[(2R)-pyrrolidin-2-ylmethoxy]phenyl}-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 323),

WO 2007/045980

PCT/IB2006/002931

- 30 -

- 3-[4-(Difluoromethoxy)-3-{[(2R)-1-propionylpyrrolidin-2-yl]methoxy}phenyl]-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 324),
- 3-[3-{[(2S)-1-acetylpyrrolidin-2-yl]methoxy}-4-(difluoromethoxy)phenyl]-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 325),
- 5 3-[3-{[(3S)-1-benzoylpyrrolidin-3-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 326),
- 3-[4-(Difluoromethoxy)-3-{[(3S)-1-propionylpyrrolidin-3-yl]oxy}phenyl]-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 327),
- (5S or 5R)-3-[3-(Benzyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 328),
- 10 2-(Benzyloxy)-4-[(5S or 5R)-1,7-dioxaspiro[4.4]non-2-en-3-yl]phenol (Compound No. 329),
- (5S or 5R)-3-[3-(Benzyloxy)-4-methoxyphenyl]-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 330),
- 15 3-{4-(Difluoromethoxy)-3-[(1-propionylpiperidin-4-yl)oxy]phenyl}-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 331),
- 3-[4-(Difluoromethoxy)-3-{[1-(4-fluorobenzoyl)piperidin-4-yl]oxy}phenyl]-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 332),
- 20 3-[3-{[1-(Cyclopropylcarbonyl)piperidin-4-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 333),
- 3-[3-{[1-(Cyclopentylcarbonyl)piperidin-4-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 334),
- 3-[4-(Difluoromethoxy)-3-{[1-[(trifluoromethyl)sulfonyl]piperidin-4-yl]oxy}phenyl]-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 335),
- 25 3-{3-[(1-Acetylpiperidin-3-yl)oxy]-4-(difluoromethoxy)phenyl}-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 336),
- 3-{4-(Difluoromethoxy)-3-[(1-propionylpiperidin-3-yl)oxy]phenyl}-1,7-dioxaspiro[4.4]non-2-ene (Compound No. 337),

WO 2007/045980

PCT/IB2006/002931

- 31 -

3-[4-(Difluoromethoxy)-3-{[1-(4-fluorobenzoyl)piperidin-3-yl]oxy}phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 338),

3-[3-{[1-(Cyclopropylcarbonyl)piperidin-3-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 339),

5 3-[3-{[1-(Cyclopentylcarbonyl)piperidin-3-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 340),

3-[4-(Difluoromethoxy)-3-{[1-(ethylsulfonyl)piperidin-3-yl]oxy}phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 341),

10 3-[3-(Benzyloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 342),

2-(Difluoromethoxy)-5-[(5*S* or 5*R*)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol (Compound No. 343), or

5-[(5*R* or 5*S*)-1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound No. 344).

15 In another embodiment, β 2-agonists can be selected from albuterol, salbutamol, biltolterol, pirbuterol, levosalbutamol, tulobuterol, terbutaline, bambuterol, metaproterenol, fenoterol, salmeterol, carmoterol, arformoterol, formoterol, or their pharmaceutically acceptable salts or solvates thereof. In yet another embodiment, corticosteroids can be selected from alclometasone, amcinonide, amelometasone, 20 beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, cloticasone, cyclomethasone, deflazacort, deprodone, dexbudesonide, diflorasone, difluprednate, fluticasone, flunisolide, halometasone, halopredone, hydrocortisone, hydrocortisone, methylprednisolone, mometasone, prednicarbate, prednisolone, rimexolone, tixocortol, triamcinolone, ulobetasol, or pharmaceutically acceptable salts or solvates thereof.

25 In another embodiment, p38 kinase inhibitors can be selected from 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-ylethoxy)naphthalen-1-yl]urea; 1-[5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(1-oxothiomorpholin-4-yl)ethoxy)naphthalen-1-yl]urea; 1-[5-tert-butyl-2-(2-methylpyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(2-pyridin-4-ylethoxy)naphthalen-1-yl]urea; 1-[5-tert-butyl-2-(2-methoxypyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-ylethoxy)naphthalen-1-yl]urea; and 1-[5-tert-butyl-2-methyl-2H-

30

WO 2007/045980

PCT/IB2006/002931

- 32 -

pyrazol-3-yl]-3-[4-(2-morpholin-4-ylethoxy)naphthalen-1-yl]urea disclosed in our co-pending United States Patent Application No. 60/605,344;

Other p38 kinase inhibitors can be selected from for example:

- tert*-Butyl 4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2*H*-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxylate (Compound No. 1a),
5 Hydrochloride salt of 6-(2-methylphenyl)-2-(piperidin-4-ylamino)-8-(tetrahydro-2*H*-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 2a),
2-[(1-Acetylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-(tetrahydro-2*H*-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 3a),
10 6-(2-Methylphenyl)-2-{{1-(methylsulfonyl)piperidin-4-yl}amino}-8-(tetrahydro-2*H*-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 4a),
2-[(1-Benzoylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-(tetrahydro-2*H*-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 5a),
N-Isopropyl-4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2*H*-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxamide (Compound
15 No. 6a),
N-(4-Fluorophenyl)-4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2*H*-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxamide (Compound
No. 7a),
20 2-{{1-(Ethylsulfonyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-8-(tetrahydro-2*H*-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 8a),
2-[(1-Benzyl-piperidin-4-yl)amino]-6-(2-methyl-phenyl)-8-(tetrahydro-2*H*-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 9a),
N-(4-Fluorophenyl)-4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2*H*-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carbothioamide (Compound
25 No. 10a),
Methylphenyl)-7-oxo-8-(tetrahydro-2*H*-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide (Compound No. 11a),

WO 2007/045980

PCT/IB2006/002931

- 33 -

- 6-(2-Methylphenyl)-2-[(1-methylpiperidin-4-yl)amino]-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 12a),
- 6-(2-Methylphenyl)-2-[(4-methylpiperazin-1-yl)amino]-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 13a),
- 5 2- {[1-(Isopropylsulfonyl)piperidin-4-yl]amino}-6-(2-methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 14a),
- tert*-Butyl 4- {[6-(2-chlorophenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}piperidine-1-carboxylate (Compound No. 15a),
- 10 6-(2-Methylphenyl)-2-(piperidin-1-ylamino)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 16a),
- 2-(Cyclobutylamino)-6-(2-methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 17a)
- 4- {[6-(2-Methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-*N*-propylpiperidine-1-carboxamide (Compound No. 18a),
- 15 *N*-[(1*S*)-1,2-Dimethylpropyl]-4- {[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}piperidine-1-carboxamide (Compound No. 19a),
- N*-Cyclohexyl-4- {[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}piperidine-1-carboxamide (Compound No. 20a),
- 20 2- {[1-(4-Fluorobenzoyl)piperidin-4-yl]amino}-6-(2-methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 21a),
- N*-(Cyclopentylmethyl)-4- {[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}piperidine-1-carboxamide (Compound No. 22a),
- 25 4- {[6-(2-Methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(1,1,3,3-tetramethylbutyl)piperidine-1-carboxamide (Compound No. 23a),

WO 2007/045980

PCT/IB2006/002931

- 34 -

- 4-{{6-(2-Methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-
d]pyrimidin-2-yl}amino}-N-octylpiperidine-1-carboxamide (Compound No. 24a),
N-Cyclopentyl-4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-
dihydropyrido[2,3-d]pyrimidin-2-yl}amino}piperidine-1-carboxamide (Compound
5 No. 25a),
N-Isopropyl-4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-
dihydropyrido[2,3-d]pyrimidin-2-yl}amino}piperidine-1-carbothioamide (Compound
No. 26a),
4-{{6-(2-Methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-
10 d]pyrimidin-2-yl}amino}-N-octylpiperidine-1-carbothioamide (Compound No. 27a),
N-tert-Butyl-4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-
dihydropyrido[2,3-d]pyrimidin-2-yl}amino}piperidine-1-carbothioamide (Compound
No. 28a),
6-(2-Methylphenyl)-2-[(1-pyrimidin-2-ylpiperidin-4-yl)amino]-8-(tetrahydro-2H-pyran-4-
15 yl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 29a),
N-Cyclopropyl-4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-
dihydropyrido[2,3-d]pyrimidin-2-yl}amino}piperidine-1-carboxamide (Compound
No. 30a),
N-[(1R)-1-Cyclohexylethyl]-4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-
20 7,8-dihydropyrido[2,3-d]pyrimidin-2-yl}amino}piperidine-1-carboxamide (Compound
No. 31a),
2-{{1-(Cyclopentylcarbonyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-8-(tetrahydro-2H-
pyran-4-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 32a),
6-(2-Methylphenyl)-2-{{1-(pyrrolidin-1-ylcarbonyl)piperidin-4-yl}amino}-8-(tetrahydro-
25 2H-pyran-4-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 33a),
6-(2-Methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)-2-(tetrahydro-2H-pyran-4-
ylamino)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 34a),
6-(2-Methylphenyl)-2-[(1,2,2,6,6-pentamethylpiperidin-4-yl)amino]-8-(tetrahydro-2H-
pyran-4-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 35a),

WO 2007/045980

PCT/IB2006/002931

- 35 -

- tert*-Butyl 4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydrofuran-3-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxylate (Compound No. 36a),
- N*-Isopropyl-4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydrofuran-3-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxamide (Compound
- 5 No. 37a),
- 6-(2-Methylphenyl)-7-oxo-2-{{1-(pyrrolidin-1-ylcarbonyl)piperidin-4-yl}amino}-1-(tetrahydrofuran-3-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-1-ium (Compound No. 38a),
- 2-{{1-(Ethylsulfonyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-7-oxo-1-(tetrahydrofuran-3-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-1-ium (Compound No. 39a),
- 10 6-(2-Methylphenyl)-2-{{1-(methylsulfonyl)piperidin-4-yl}amino}-8-(tetrahydrofuran-3-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 40a),
- N*-Cyclopropyl-4-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydrofuran-3-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxamide (Compound
- No. 41a),
- 15 6-(2-Methylphenyl)-2-{{(3*S*)-1-(methylsulfonyl)pyrrolidin-3-yl}amino}-8-(tetrahydrofuran-3-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 42a),
- tert*-Butyl 4-({6-(2-methylphenyl)-7-oxo-8-[(3*S*)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxylate (Compound
- No. 43a),
- 20 6-(2-Methylphenyl)-2-{{1-(methylsulfonyl)piperidin-4-yl}amino}-8-[(3*S*)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 44a),
- N*-Isopropyl-4-({6-(2-methylphenyl)-7-oxo-8-[(3*S*)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxamide (Compound
- No. 45a),
- 25 6-(2-Methylphenyl)-2-{{1-(methylsulfonyl)piperidin-4-yl}amino}-8-[(3*R*)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 46a),
- N*-Isopropyl-4-({6-(2-methylphenyl)-7-oxo-8-[(3*R*)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxamide (Compound
- No. 47a),

WO 2007/045980

PCT/IB2006/002931

- 36 -

tert-Butyl 4-({6-(2-methylphenyl)-7-oxo-8-[(3R)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxylate (Compound No. 48a),

Hydrochloride salt of 6-(2-methylphenyl)-2-(piperidin-4-ylamino)-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 49a),

Hydrochloride salt 6-(2-methylphenyl)-2-(piperidin-4-ylamino)-8-[(3S)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 50a),

2-{{1-(Ethylsulfonyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-8-[(3S)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 51a),

N-Cyclopropyl-4-({6-(2-methylphenyl)-7-oxo-8-[(3S)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxamide (Compound No. 52a),

N-Cyclopropyl-4-({6-(2-methylphenyl)-7-oxo-8-[(3R)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxamide (Compound No. 53a),

2-[(1-Benzylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 54a),

2-(Cyclobutylamino)-6-(2-methylphenyl)-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 55a),

2-(Cyclopropylamino)-6-(2-methylphenyl)-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 56a),

2-{{1-(Ethylsulfonyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 57a),

2-[(1-Acetylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 58a),

2-{{1-(4-Fluorobenzoyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 59a),

2-{{1-(Cyclopropylcarbonyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 60a),

WO 2007/045980

PCT/IB2006/002931

- 37 -

- 2-[[1-(Cyclopropylcarbonyl)piperidin-4-yl]amino]-6-(2-methylphenyl)-8-[(3S)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 61a),
- 2-[[1-(Cyclopentylcarbonyl)piperidin-4-yl]amino]-6-(2-methylphenyl)-8-[(3S)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 62a),
- 5 2-[[1-(Cyclopentylcarbonyl)piperidin-4-yl]amino]-6-(2-methylphenyl)-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 63a),
- 2-[(1-Benzoylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-[(3S)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 64a),
- 2-[(1-Benzoylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 65a),
- 10 2-[[1-(4-Fluorobenzoyl)piperidin-4-yl]amino]-6-(2-methylphenyl)-8-[(3S)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 66a),
- N*-(4-Fluorophenyl)-4-({6-(2-methylphenyl)-7-oxo-8-[(3R)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxamide
- 15 (Compound No. 67a),
- 2-[(1-Acetylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-[(3S)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 68a),
- N*-(4-Fluorophenyl)-4-({6-(2-methylphenyl)-7-oxo-8-[(3S)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxamide (Compound
- 20 No. 69a),
- tert*-Butyl (3S)-3-({6-(2-methylphenyl)-7-oxo-8-[(3R)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxylate
- (Compound No. 70a),
- (3S)-*N*-Isopropyl-3-({6-(2-methylphenyl)-7-oxo-8-[(3R)-tetrahydrofuran-3-yl]-7,8-
- 25 dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxamide
- (Compound No. 71a)
- tert*-Butyl (3S)-3-({6-(2-methylphenyl)-7-oxo-8-[(3S)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxylate (Compound
- No. 72a),

WO 2007/045980

PCT/IB2006/002931

- 38 -

- tert*-Butyl (3R)-3-({6-(2-methylphenyl)-7-oxo-8-[(3R)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxylate (Compound No. 73a),
- (3R)-*N*-Isopropyl-3-({6-(2-methylphenyl)-7-oxo-8-[(3R)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxamide (Compound No. 74a),
- (3S)-*N*-Isopropyl-3-({6-(2-methylphenyl)-7-oxo-8-[(3S)-tetrahydrofuran-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxamide (Compound No. 75a),
- 6-(2-Methylphenyl)-2-{{[(3S)-1-(methylsulfonyl)piperidin-3-yl] amino}-8-[(3S)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 76a),
- 6-(2-Methylphenyl)-2-{{[1-(methylsulfonyl)piperidin-4-yl] amino}-8-[(3S)-1-(methylsulfonyl)pyrrolidin-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 77a),
- 6-(2-Methylphenyl)-2-{{[1-(methylsulfonyl)piperidin-4-yl] amino}-8-[(3S)-1-(methylsulfonyl)pyrrolidin-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 78a),
- tert*-Butyl 4-({6-(2-methylphenyl)-7-oxo-8-[(3S)-pyrrolidin-3-yl]-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxylate (Compound No. 79a)
- 4-({8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)-*N*-isopropylpiperidine-1-carboxamide (Compound No. 80a),
- Hydrochloride salt of 8-[(3S)-1-acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-2-(piperidin-4-ylamino)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 81a),
- tert*-Butyl (3S)-3-{{[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl] amino}pyrrolidine-1-carboxylate (Compound No. 82a),
- (3S)-*N*-Isopropyl-3-{{[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl] amino}pyrrolidine-1-carboxamide (Compound No. 83a),

WO 2007/045980

PCT/IB2006/002931

- 39 -

(3S)-*N*-Isopropyl-3-{{[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}pyrrolidine-1-carbothioamide (Compound No. 84a),

6-(2-Methylphenyl)-2-{{[(3S)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 85a),

2-{{[(3S)-1-(Ethylsulfonyl)pyrrolidin-3-yl]amino}-6-(2-methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 86a),

2-{{[(3S)-1-Acetylpyrrolidin-3-yl]amino}-6-(2-methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 87a),

10 (3S)-*N*-Cyclopropyl-3-{{[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}pyrrolidine-1-carboxamide (Compound No. 88a),

(3S)-*N*-Butyl-3-{{[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}pyrrolidine-1-carboxamide (Compound
15 No. 90a),

(3S)-*N*-Cyclopentyl-3-{{[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}pyrrolidine-1-carboxamide (Compound No. 91a),

(3S)-*N*-[(1S)-1,2-Dimethylpropyl]-3-{{[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}pyrrolidine-1-carboxamide
20 (Compound No. 92a),

2-{{[(3R)-1-Benzylpyrrolidin-3-yl]amino}-6-(2-methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 93a),

2-{{[(3S)-1-Benzylpyrrolidin-3-yl]amino}-6-(2-methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 94a),
25

(3S)-*N*-Cyclohexyl-3-{{[6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}pyrrolidine-1-carboxamide (Compound No. 95a),

WO 2007/045980

PCT/IB2006/002931

- 40 -

- (3S)-3-{{6-(2-Methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-octylpyrrolidine-1-carboxamide (Compound No. 96a),
- 2-{{[(3S)-1-(Cyclopropylcarbonyl)pyrrolidin-3-yl]amino}-6-(2-methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 97a),
- 5 2-{{[(3S)-1-(Cyclopentylcarbonyl)pyrrolidin-3-yl]amino}-6-(2-methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 98a),
- 6-(2-Methylphenyl)-2-{{[(3S)-1-pyrimidin-2-yl-pyrrolidin-3-yl]amino}-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 99a)
- 10 (3S)-*N*-[(1R)-1-Cyclohexylethyl]-3-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydro-2H-pyran-4-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}pyrrolidine-1-carboxamide (Compound No. 100a),
- 6-(2-Methylphenyl)-2-{{[(3S)-1-(pyrrolidin-1-ylcarbonyl)pyrrolidin-3-yl]amino}-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 101a),
- 2-{{[(3S)-1-(Cyclopentylacetyl)pyrrolidin-3-yl]amino}-6-(2-methylphenyl)-8-(tetrahydro-2H-pyran-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 102a),
- 15 *tert*-Butyl (3S)-3-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydrofuran-3-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}pyrrolidine-1-carboxylate (Compound No. 103a),
- tert*-Butyl 4-{{8-[(3S)-1-benzylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxylate (Compound No. 104a),
- 20 (3S)-*N*-Isopropyl-3-{{6-(2-methylphenyl)-7-oxo-8-(tetrahydrofuran-3-yl)-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}pyrrolidine-1-carboxamide (Compound No. 105a),
- 25 *tert*-Butyl 4-{{8-(1-benzylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxylate (Compound No. 106a),

WO 2007/045980

PCT/IB2006/002931

- 41 -

tert-Butyl 4-{{6-(2-methylphenyl)-8-(1-methylpiperidin-4-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxylate (Compound No. 107a)

5 8-(1-Benzylpiperidin-4-yl)-6-(2-methylphenyl)-2-[(1-methylpiperidin-4-yl)amino]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 108a),

8-(1-Benzylpiperidin-4-yl)-2-(cyclobutylamino)-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 109a),

10 *tert*-Butyl (3S)-3-{{8-(1-benzylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}pyrrolidine-1-carboxylate (Compound No. 110a),

(3S)-3-{{8-(1-Benzylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-isopropylpyrrolidine-1-carboxamide (Compound No. 111a),

Hydrochloride salt of 8-(1-benzylpiperidin-4-yl)-6-(2-methylphenyl)-2-(piperidin-4-ylamino)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 112a),

15 Hydrochloride salt of 6-(2-methylphenyl)-8-(1-methylpiperidin-4-yl)-2-(piperidin-4-ylamino)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 113a),

4-{{8-(1-Benzylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-isopropylpiperidine-1-carboxamide (Compound No. 114a),

20 4-{{8-(1-Benzylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-cyclohexylpiperidine-1-carboxamide (Compound No. 115a),

4-{{8-(1-Benzylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-cyclopentylpiperidine-1-carboxamide (Compound No. 116a),

4-{{8-(1-Benzylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-isobutylpiperidine-1-carboxamide (Compound No. 117a),

25 4-{{8-(1-Benzylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-[(1R)-1-cyclohexylethyl]piperidine-1-carboxamide (Compound No. 118a),

WO 2007/045980

PCT/IB2006/002931

- 42 -

N-Isopropyl-4-{{6-(2-methylphenyl)-8-(1-methylpiperidin-4-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxamide (Compound No. 119a),

N-Cyclopropyl-4-{{6-(2-methylphenyl)-8-(1-methylpiperidin-4-yl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxamide (Compound No. 120a),

8-(1-Benzylpiperidin-4-yl)-2-{{1-(cyclopentylacetyl)piperidin-4-yl}amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 121a),

8-(1-Benzylpiperidin-4-yl)-2-{{1-(cyclopropylcarbonyl)piperidin-4-yl}amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 122a),

8-(1-Benzylpiperidin-4-yl)-6-(2-methylphenyl)-2-{{1-(phenylsulfonyl)piperidin-4-yl}amino}pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 123a),

8-(1-Benzylpiperidin-4-yl)-6-(2-methylphenyl)-2-{{1-(methylsulfonyl)piperidin-4-yl}amino}pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 124a),

8-(1-Benzylpiperidin-4-yl)-2-{{1-(ethylsulfonyl)piperidin-4-yl}amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound no. 125a),

6-(2-Methylphenyl)-8-(1-methylpiperidin-4-yl)-2-{{1-(methylsulfonyl)piperidin-4-yl}amino}pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 126a),

2-{{1-(Ethylsulfonyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-8-(1-methylpiperidin-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 127a),

2-{{1-(Isopropylsulfonyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-8-(1-methylpiperidin-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 128a),

6-(2-Methylphenyl)-8-(1-methylpiperidin-4-yl)-2-{{1-(pyrrolidin-1-ylcarbonyl)piperidin-4-yl}amino}pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 129a),

2-[(1-Benzoylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-(1-methylpiperidin-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 130a),

2-[(1-Benzoylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-(1-methylpiperidin-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 130a),

WO 2007/045980

PCT/IB2006/002931

- 43 -

- tert*-Butyl 4-{{6-(2-methylphenyl)-7-oxo-8-piperidin-4-yl-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxylate (Compound No. 131a),
- 6-(2-Methylphenyl)-8-piperidin-4-yl-2-(piperidin-4-ylamino)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 132a),
- 5 *N*-Isopropyl-4-{{6-(2-methylphenyl)-7-oxo-8-piperidin-4-yl-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxamide (Compound No. 133a),
- tert*-Butyl 4-{{8-{1-[(isopropylamino)carbonyl]piperidin-4-yl}-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}piperidine-1-carboxylate (Compound No. 134a),
- 10 Hydrochloride salt of *N*-isopropyl-4-[6-(2-methylphenyl)-7-oxo-2-(piperidin-4-ylamino)pyrido[2,3-*d*]pyrimidin-8(7H)-yl]piperidine-1-carboxamide (Compound No. 135a),
- N*-Isopropyl-4-[2-({1-[(isopropylamino)carbonyl]piperidin-4-yl}amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]piperidine-1-carboxamide
- 15 (Compound No. 136a),
- 4-[2-({1-[(Cyclopropylamino)carbonyl]piperidin-4-yl}amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 137a),
- 4-[2-({1-[(*tert*-Butylamino)carbonyl]piperidin-4-yl}amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound
- 20 No. 138a),
- 4-[2-({1-[(Cyclohexylamino)carbonyl]piperidin-4-yl}amino)-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 139a),
- 25 *N*-Isopropyl-4-[6-(2-methylphenyl)-2-{{1-(morpholin-4-ylcarbonyl)piperidin-4-yl}amino}-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]piperidine-1-carboxamide (Compound No. 140a),
- 4-[2-{{1-(4-Fluorobenzoyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 141a),

WO 2007/045980

PCT/IB2006/002931

- 44 -

- N*-Isopropyl-4-[6-(2-methylphenyl)-2-[[1-(methylsulfonyl)piperidin-4-yl]amino]-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]piperidine-1-carboxamide (Compound No. 142a),
- 4-[2-[[1-(Ethylsulfonyl)piperidin-4-yl]amino]-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 143a),
- 5 *N*-Isopropyl-4-[2-[[1-(isopropylsulfonyl)piperidin-4-yl]amino]-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]piperidine-1-carboxamide (Compound No. 144a),
- 4-[2-[[1-(Cyclopropylcarbonyl)piperidin-4-yl]amino]-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 145a),
- 10 4-[2-[(1-Benzoylpiperidin-4-yl)amino]-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 146a),
- 4-[2-[(1-Acetylpiperidin-4-yl)amino]-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 147a),
- N*-Isopropyl-4-[6-(2-methylphenyl)-2-[(1-methylpiperidin-4-yl)amino]-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]piperidine-1-carboxamide (Compound No. 148a),
- 15 4-[2-[(1-Benzylpiperidin-4-yl)amino]-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 149a),
- 8-(1-Acetylpiperidin-4-yl)-2-[(1-acetylpiperidin-4-yl)amino]-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 150a),
- 20 4-[2-[[1-(4-Fluorobenzoyl)piperidin-4-yl]amino]-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 151a),
- tert*-Butyl 4-({6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxylate (Compound No. 152a),
- 25 Hydrochloride salt of 6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]-2-(piperidin-4-ylamino)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 153a),
- N*-Isopropyl-4-({6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino)piperidine-1-carboxamide (Compound No. 154a),

WO 2007/045980

PCT/IB2006/002931

- 45 -

N-(*tert*-Butyl)-4-({6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxamide (Compound No. 155a),

5 *N*-Cyclohexyl-4-({6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxamide (Compound No. 156a),

N-(4-Fluorophenyl)-4-({6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxamide (Compound No. 157a),

10 6-(2-Methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]-2-{{1-(morpholin-4-ylcarbonyl)piperidin-4-yl} amino}pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 158a),

6-(2-Methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]-2-{{1-(methylsulfonyl)piperidin-4-yl} amino}pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 159a),

15 2-{{1-(Ethylsulfonyl)piperidin-4-yl} amino}-6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 160a),

2-{{1-(Isopropylsulfonyl)piperidin-4-yl} amino}-6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 161a),

20 2-{{1-(Cyclopropylcarbonyl)piperidin-4-yl} amino}-6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound 162a),

2-[(1-Acetylpiperidin-4-yl) amino]-6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 163a),

2-[(1-Benzoylpiperidin-4-yl) amino]-6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 164a),

25 2-{{1-(4-Fluorobenzoyl)piperidin-4-yl} amino}-6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 165a),

tert-Butyl 4-{{8-(1-acetylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino}piperidine-1-carboxylate (Compound No. 166a),

WO 2007/045980

PCT/IB2006/002931

- 46 -

- 8-(1-Acetylpiperidin-4-yl)-6-(2-methylphenyl)-2-(piperidin-4-ylamino)pyrido[2,3-
d]pyrimidin-7(8H)-one (Compound No. 167a),
- 4-{{[8-(1-Acetylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-
d]pyrimidin-2-yl]amino}-N-isopropylpiperidine-1-carboxamide (Compound No. 168a),
- 5 4-{{[8-(1-Acetylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-
d]pyrimidin-2-yl]amino}-N-cyclopropylpiperidine-1-carboxamide (Compound No. 169a),
- 4-{{[8-(1-Acetylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-
d]pyrimidin-2-yl]amino}-N-(tert-butyl)piperidine-1-carboxamide (Compound No. 170a),
- 10 4-{{[8-(1-Acetylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-
d]pyrimidin-2-yl]amino}-N-cyclohexylpiperidine-1-carboxamide (Compound No. 171a),
- 4-{{[8-(1-Acetylpiperidin-4-yl)-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-
d]pyrimidin-2-yl]amino}-N-(4-fluorophenyl)piperidine-1-carboxamide (Compound
No. 172a),
- 8-(1-Acetylpiperidin-4-yl)-6-(2-methylphenyl)-2-{{[1-(morpholin-4-ylcarbonyl)piperidin-
15 4-yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 173a),
- 8-(1-Acetylpiperidin-4-yl)-6-(2-methylphenyl)-2-{{[1-(methanesulfonyl)piperidin-4-
yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 174a),
- 8-(1-Acetylpiperidin-4-yl)-2-{{[1-(ethanesulfonyl)piperidin-4-yl]amino}-6-(2-
methylphenyl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 175a),
- 20 8-(1-Acetylpiperidin-4-yl)-2-{{[1-(isopropylsulfonyl)piperidin-4-yl]amino}-6-(2-
methylphenyl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 176a),
- 8-(1-Acetylpiperidin-4-yl)-2-{{[1-(cyclopropylcarbonyl)piperidin-4-yl]amino}-6-(2-
methylphenyl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 177a),
- 8-(1-Acetylpiperidin-4-yl)-2-{{[1-(4-fluorobenzoyl)piperidin-4-yl]amino}-6-(2-
25 methylphenyl)pyrido[2,3-d]pyrimidin-7(8H)-one (Compound No. 178a),
- tert-Butyl 4-{{[8-[(3S)-1-acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-
dihydropyrido[2,3-d]pyrimidin-2-yl]amino}piperidine-1-carboxylate (Compound
No. 179a),

WO 2007/045980

PCT/IB2006/002931

- 47 -

- Hydrochloride salt of 8-[(3S)-1-acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-2-(piperidin-4-ylamino)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 180a),
- 8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-2-[[1-(methylsulfonyl)piperidin-4-yl]amino]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 181a),
- 5 2-[(1-Acetylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-(1-methylpiperidin-4-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 182a),
- Hydrochloride salt of 6-(2-methylphenyl)-8-[(3S)-1-(methylsulfonyl)pyrrolidin-3-yl]-2-(piperidin-4-ylamino)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 183a),
- tert*-Butyl 4-[[8-[(3R)-1-acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-
- 10 dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino]piperidine-1-carboxylate (Compound No. 184a),
- Hydrochloride salt of 6-(2-methylphenyl)-2-[(3S)-pyrrolidin-3-ylamino]-8-(tetrahydrofuran-3-yl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 185a),
- Hydrochloride salt of 6-(2-methylphenyl)-2-[(3S)-piperidin-3-ylamino]-8-[(3R)-
- 15 tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 186a),
- Hydrochloride salt of 6-(2-methylphenyl)-2-[(3S)-piperidin-3-ylamino]-8-[(3S)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 187a),
- Hydrochloride salt of 6-(2-methylphenyl)-2-[(3R)-piperidin-3-ylamino]-8-[(3R)-tetrahydrofuran-3-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 188a),
- 20 4-[2-[(1-[[[(4-Fluorophenyl)amino]carbonyl]piperidin-4-yl)amino]-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 189a),
- 4-[[8-{1-[(Isopropylamino)carbonyl]piperidin-4-yl}-6-(2-methylphenyl)-7-oxo-7,8-
- dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino]-*N*-morpholin-4-ylpiperidine-1-carboxamide
- 25 (Compound No. 190a),
- 4-[2-[[1-(2,2-Dimethylpropanoyl)piperidin-4-yl]amino]-6-(2-methylphenyl)-7-oxopyrido[2,3-*d*]pyrimidin-8(7H)-yl]-*N*-isopropylpiperidine-1-carboxamide (Compound No. 191a),

WO 2007/045980

PCT/IB2006/002931

- 48 -

- 8-[(3S)-1-Acetylpyrrolidin-3-yl]-2-[(1-benzylpiperidin-4-yl)amino]-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 192a),
- N*-Cyclopropyl-4-({6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)piperidine-1-carboxamide (Compound
- 5 No. 193a),
- 4-({6-(2-Methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl} amino)-*N*-morpholin-4-ylpiperidine-1-carboxamide (Compound No. 194a),
- 2-{{1-(2,2-Dimethylpropanoyl)piperidin-4-yl}amino}-6-(2-methylphenyl)-8-[1-
- 10 (methylsulfonyl)piperidin-4-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 195a),
- 6-(2-Methylphenyl)-2-[(1-methylpiperidin-4-yl)amino]-8-[1-(methylsulfonyl)piperidin-4-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 196a),
- 2-[(1-Benzylpiperidin-4-yl)amino]-6-(2-methylphenyl)-8-[1-(methylsulfonyl)piperidin-4-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 197a),
- 15 8-(1-Acetylpiperidin-4-yl)-2-[(1-benzoylpiperidin-4-yl)amino]-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 198a),
- 8-(1-Acetylpiperidin-4-yl)-2-{{1-(2,2-dimethylpropanoyl)piperidin-4-yl}amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 199a),
- 8-(1-Acetylpiperidin-4-yl)-6-(2-methylphenyl)-2-[(1-methylpiperidin-4-
- 20 yl)amino]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 200a),
- 8-(1-Acetylpiperidin-4-yl)-2-[(1-benzylpiperidin-4-yl)amino]-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 201a),
- 4-{{8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-cyclopropylpiperidine-1-carboxamide (Compound No. 202a),
- 25 4-{{8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-(*tert*-butyl)piperidine-1-carboxamide (Compound No. 203a),
- 4-{{8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl}amino}-*N*-cyclohexylpiperidine-1-carboxamide (Compound No. 204a),

WO 2007/045980

PCT/IB2006/002931

- 49 -

- 4-{{8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(4-fluorophenyl)piperidine-1-carboxamide (Compound No. 205a),
- 4-{{8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-*N*-morpholin-4-ylpiperidine-1-carboxamide (Compound No. 206a),
- 8-[(3S)-1-Acetylpyrrolidin-3-yl]-2-{{1-(ethylsulfonyl)piperidin-4-yl]amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 207a),
- 8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-2-{{1-(propylsulfonyl)piperidin-4-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8H)-one ((Compound No. 208a),
- 8-[(3R)-1-Acetylpyrrolidin-3-yl]-2-{{1-(cyclopropylcarbonyl)piperidin-4-yl]amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 209a),
- 2-[(1-Acetylpiperidin-4-yl)amino]-8-[(3R)-1-acetylpyrrolidin-3-yl]-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 210a),
- 8-[(3R)-1-Acetylpyrrolidin-3-yl]-2-[(1-benzoylpiperidin-4-yl)amino]-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 211a),
- 8-[(3R)-1-Acetylpyrrolidin-3-yl]-2-{{1-(4-fluorobenzoyl)piperidin-4-yl]amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 212a),
- 8-[(3R)-1-Acetylpyrrolidin-3-yl]-2-{{1-(2,2-dimethylpropanoyl)piperidin-4-yl]amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 213a),
- 8-[(3R)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-2-[(1-methylpiperidin-4-yl)amino]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 214a),
- 8-[(3R)-1-Acetylpyrrolidin-3-yl]-2-[(1-benzylpiperidin-4-yl)amino]-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 215a),
- tert*-Butyl 4-{{8-[(3S)-1-acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}piperidine-1-carboxylate (Compound No. 216a),
- 8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-2-[(1-methylpiperidin-4-yl)amino]pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 217a),

WO 2007/045980

PCT/IB2006/002931

- 50 -

- 4-{{[8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-*N*-isopropylpiperidine-1-carboxamide (Compound No. 218a),
- 4-{{[8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-*N*-cyclopropylpiperidine-1-carboxamide (Compound No. 219a),
- 5 4-{{[8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(*tert*-butyl)piperidine-1-carboxamide (Compound No. 220a),
- 4-{{[8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-*N*-cyclohexylpiperidine-1-carboxamide (Compound No. 221a)
- 10 4-{{[8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-*N*-(4-fluorophenyl)piperidine-1-carboxamide (Compound No. 222a),
- 4-{{[8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}-*N*-morpholin-4-ylpiperidine-1-carboxamide (Compound No. 223a),
- 15 8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-2-{{[1-(methylsulfonyl)piperidin-4-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 224a),
- 8-[(3S)-1-Acetylpyrrolidin-3-yl]-2-{{[1-(ethylsulfonyl)piperidin-4-yl]amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 225a),
- 8-[(3S)-1-Acetylpyrrolidin-3-yl]-6-(2-methylphenyl)-2-{{[1-(propylsulfonyl)piperidin-4-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 226a),
- 20 8-[(3S)-1-Acetylpyrrolidin-3-yl]-2-{{[1-(cyclopropylcarbonyl)piperidin-4-yl]amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 227a),
- 2-[(1-Acetylpyrrolidin-4-yl)amino]-8-[(3S)-1-acetylpyrrolidin-3-yl]-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 228a),
- 25 8-[(3S)-1-Acetylpyrrolidin-3-yl]-2-[(1-benzoylpiperidin-4-yl)amino]-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 229a),
- 8-[(3S)-1-Acetylpyrrolidin-3-yl]-2-{{[1-(4-fluorobenzoyl)piperidin-4-yl]amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 230a),

WO 2007/045980

PCT/IB2006/002931

- 51 -

8-[(3S)-1-Acetylpyrrolidin-3-yl]-2-[[1-(2,2-dimethylpropanoyl)piperidin-4-yl]amino}-6-(2-methylphenyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (Compound No. 231a) disclosed in our copending patent application\ No. 2602/DEL/2005;

and the compounds which are disclosed in United States Patent Application No.

5 60/598621, 60/630,517, 1098/DEL/2005 and 211/DEL/2005. The p38 MAP Kinase inhibitors can also be selected from compounds not limited to those described in WO98/47892, WO00/43384, and WO98/27098.

Examples of p38 MAP Kinase inhibitors include, but are not limited to, Vx-745, as disclosed in WO 98/27098, BIRB-796, as disclosed in WO 00/43384, RWJ-67657, as
10 disclosed in WO 98/47892, and SB – 239063, as disclosed in WO 97/25048. Any reference to the above mentioned p38 kinase inhibitors also include any pharmacologically acceptable acid addition salts thereof which may exist. By the physiologically or pharmacologically acceptable acid addition salts thereof which may be formed by the p38 kinase inhibitors are meant, according to the invention, pharmaceutically acceptable salts
15 selected from among the salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, and maleic acid.

In another embodiment, corticosteroids can be selected from alclometasone, amcinonide, amelometasone, beclometasone, betamethasone, budesonide, ciclesonide,
20 clobetasol, cloticasone, cyclomethasone, deflazacort, deprodone, dexamethasone, diflorasone, difluprednate, fluticasone, flunisolide, halometasone, halopredone, hydrocortisone, hydrocortisone, methylprednisolone, mometasone, prednicarbate, prednisolone, rimexolone, tixocortol, triamcinolone, tolterodine, oxybutynin, ulobetasol, rofleponide, KSR 592, as disclosed in US Patent 4,285,937, ST-126, as disclosed in EP
25 1344526, dexamethasone and pharmaceutically acceptable salts, solvates thereof. Preferred corticosteroids include, for example, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, and dexamethasone, while budesonide, fluticasone, mometasone, ciclesonide. Examples of possible salts or derivatives include: sodium salts, sulfobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen
30 phosphates, palmitates, pivalates, or furoates. In some cases, the corticosteroids may also occur in the form of their hydrates.

WO 2007/045980

PCT/IB2006/002931

- 52 -

The one or more PDE-IV and one or more muscarinic receptor antagonists (MRA) can be present in compositions described herein in a ratio from 1:10 to 10:1.

The one or more PDE-IV and one or more β 2-agonist can be present in compositions described herein in a ratio from 1:10 to 10:1.

The one or more PDE-IV and one or more p38 MAP Kinase inhibitors can be present in compositions described herein in a ratio from 1:10 to 10:1.

The one or more PDE-IV and one or more corticosteroids can be present in compositions described herein in a ratio from 1:10 to 10:1.

In another aspect, provided herein are methods of treating autoimmune, inflammatory or allergic diseases or disorders, comprising administering one or more pharmaceutical compositions described herein. The autoimmune, inflammatory or allergic diseases or disorders can be selected from respiratory disorder, asthma, chronic bronchitis, chronic obstructive pulmonary disease, whooping cough, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, eczema, inflammatory bowel disease, endotoxic shock, anaphylactic shock, laminitis in horses, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, periodontitis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, transplant rejection, rhinitis, pruritus, diabetes insipidus, eye diseases, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, orthrosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, osteoporosis, osteoarthritis, inflammation, ankylosing spondylitis, transplant rejection, graft versus host disease, hypersecretion of gastric acid, bacterial, fungal induced sepsis, viral induced sepsis, fungal induced septic shock, viral induced septic shock, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression memory impairment, tumor growth, cancerous invasion of normal tissues Hashimoto's thyroiditis (underactive thyroid), Graves' disease (overactive thyroid), Lupus and acquired immuno deficiency syndrome.

WO 2007/045980

PCT/IB2006/002931

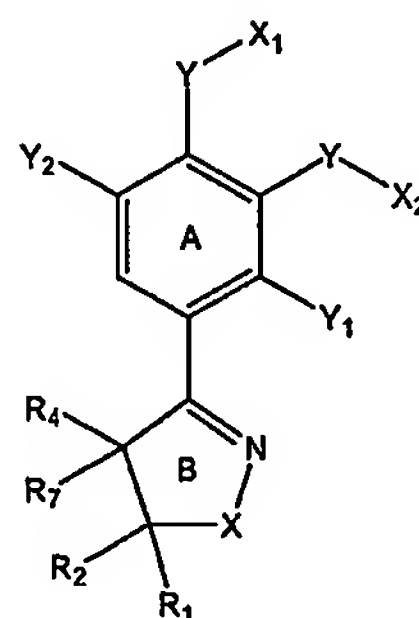
- 53 -

Detailed Description of the Invention

In accordance with an aspect, provided herein are compositions comprising one or more PDE-IV inhibitors and at least one other active ingredient such as muscarinic receptor antagonists (MRA), β 2-agonists, p38 MAP Kinase inhibitors and corticosteroids and optionally one or more pharmaceutically acceptable excipients wherein the PDE-IV is

wherein:

a. Formula Ia is:



FORMULA Ia

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides, wherein

When X is oxygen,

R₁ can be hydrogen, alkyl, heterocyclyl, $-(CH_2)_mC(=O)R_3$, or $(CH_2)_{1-4}OR'$, (wherein m is an integer 0-2, R₃ can be alkyl, cycloalkyl, heterocyclyl, or optionally substituted R_p or R_q, wherein R_p can be heterocyclyl or heteroaryl ring, wherein the rings are attached to $(CH_2)_mC(=O)$ through N, and R_q can be heterocyclyl or heteroaryl ring wherein the rings are attached to $-(CH_2)_mC(=O)$ through C, and wherein R' can be can be alkyl, alkenyl, alkynyl, saturated or unsaturated cycloalkyl, aryl, heterocyclyl or heteroaryl);

R₂ can be $(CH_2)_mC(=O)R_3$, $-(CH_2)_{1-4}OR'$, or $C(=O)NR_xR_y$ {where m, R₃ and R' are as defined above, and wherein R_x and R_y each independently can be hydrogen, alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, cycloalkyl, carboxy, $-S(O)_mR_5$ (wherein R₅ can be hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl,

WO 2007/045980

PCT/IB2006/002931

- 54 -

- heteroarylalkyl, heterocyclyl or heterocyclylalkyl), aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl}, or R_1 and R_2 together form an optionally substituted cycloalkyl or heterocyclyl ring wherein the optional substituent is oxo, alkyl, alkenyl, alkynyl, halogen, nitro, $-NH_2$, $-NHC(=O)OR_6$, $-C(=O)NR_xR_y$, cyano, hydroxy, alkoxy, or substituted amino (wherein R_6 can be alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclylalkyl), with the proviso that if R_1 is $-(CH_2)_{1-4}OR'$, then R_2 is also $-(CH_2)_{1-4}OR'$, and with the proviso that if R_1 is $C(=O)NR_xR_y$, then R_2 is also $C(=O)NR_xR_y$;
- R_4 can be hydrogen; alkyl; $-OR_5$; halogen; $-NH_2$, substituted amino; cyano; carboxy; or $-C(=O)NR_xR_y$ (wherein R_5 , R_x and R_y are as defined above); or R_2 and R_4 forms an optionally substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s) selected from the group consisting of N, O and S, wherein the substituents can be one or more of alkyl, halogen, hydroxy, alkoxy, $-NH_2$ or substituted amino (wherein R_3 and R_x and R_y are as defined above), with the proviso that R_2 and R_4 together does not form $-CH_2-O-CH_2-O-CH_2-$;
- R_7 can be hydrogen, alkyl, alkenyl, alkynyl, $-OR_5$, halogen, cyano, $-NH_2$, or substituted amino;
- X_1 and X_2 each independently can be hydrogen, alkyl, alkaryl, cycloalkyl, alkaryl, alkenyl, cycloalkylalkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, $-(CH_2)_gC(=O)NR_xR_y$, $-(CH_2)_{g1}C(=O)OR_3$ or heteroarylalkyl; wherein g_1 can be an integer from 1-3 (wherein R_x , R_y , g and R_3 are as defined above);
- Y can each independently be an oxygen atom; a sulphur atom; or $-NR$ (wherein R can be can be hydrogen, acyl, aryl, or alkyl);
- Y_1 and Y_2 each independently can be hydrogen; alkyl; $-OR$; $-SR$; or $-NHR$ (wherein R is as defined above);
- wherein any of Y_1 and X_2 & X_1 and Y_2 together optionally form a ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms such as N, O and S, and X_1 and X_2 can together optionally form a ring fused with ring A, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms such as N, O or S, and

WO 2007/045980

PCT/IB2006/002931

- 55 -

When X is NR₇, or S (wherein R₇ can be hydrogen, or C₁₋₆ alkyl)

- R₁ and R₂** can each independently be alkyl, alkenyl, alkynyl, alkoxy, hydroxy, cyano, nitro, halogen, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, NH₂, substituted amino, carboxy, -(CH₂)_mC(=O)R₃, -C(=O)NR_xR_y, or (CH₂)₁₋₄OR',
 5 {wherein m is an integer 0-2, R₃ can be alkyl, cycloalkyl, heterocyclyl, or optionally substituted R_p or R_q (wherein R_p can be heterocyclyl or heteroaryl ring, wherein the rings are attached to (CH₂)_mC(=O) through N, and R_q can be heterocyclyl or heteroaryl ring wherein the rings are attached to -(CH₂)_mC(=O) through C), wherein R' can be can be alkyl, alkenyl, alkynyl, saturated or unsaturated cycloalkyl, aryl, heterocyclyl or heteroaryl, and wherein R_x and R_y each independently can be hydrogen, alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, cycloalkyl, carboxy, -S(O)_mR₅ (wherein R₅ can be hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl), aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, or
 15 heterocyclylalkyl}, or **R₁ and R₂** together can form an optionally substituted cycloalkyl or heterocyclyl ring wherein the optional substituent is oxo, alkyl, alkenyl, alkynyl, halogen, nitro, -NH₂, -NHC(=O)OR₆ (wherein R₆ can be alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclylalkyl), -
 20 C(=O)NR_xR_y, cyano, hydroxy, alkoxy, or substituted amino;
- R₄** can be hydrogen; alkyl; -OR₅; halogen; -NH₂, substituted amino; cyano; carboxy; or -C(=O)NR_xR_y (wherein R₅, R_x and R_y are as defined above); or **R₂ and R₄** forms an optionally substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s) selected from the
 25 group consisting of N, O and S, wherein the substituents can be one or more of alkyl, halogen, hydroxy, alkoxy or substituted amino (wherein R₃ and R_x and R_y are as defined above), with the proviso that R₂ and R₄ together does not form -CH₂-O-CH₂-O-CH₂-;
- R₇** can be hydrogen, alkyl, alkenyl, alkynyl, -OR₅, halogen, cyano, -NH₂, or
 30 substituted amino;

WO 2007/045980

PCT/IB2006/002931

- 56 -

X_1 and X_2 each independently can be alkyl, cycloalkyl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl;

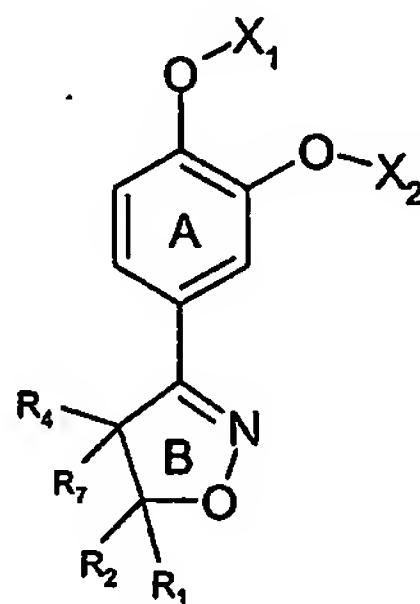
Y can each independently be an oxygen atom; a sulphur atom; or $-NR$ (wherein R can be can be hydrogen, acyl, aryl, or alkyl);

5 Y_1 and Y_2 each independently can be hydrogen, alkyl, $-OR$, $-SR$, or $-NHR$ (wherein R is as defined above);

wherein any of Y_1 and X_2 & X_1 and Y_2 together optionally form a ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms such as N, O and S;

10 X_1 and X_2 can together optionally forms a cyclic ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms such as N, O or S.

b. Formula Ib is:



Formula Ib

15

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides, wherein

R_1 and R_2 together forms an optionally substituted cycloalkyl or heterocyclyl ring wherein one or more optional substituent are oxo, alkyl, alkaryl, alkenyl, alkynes, heterocyclylalkyl, cycloalkylalkyl, $-SO_2NR_xR_y$, halogen, $-NH_2$, $-(CH_2)_gC(=O)NR_xR_y$, $-NHC(=O)OR_6$, $-NHC(=O)NR_xR_y$, $-C(=O)OR_3$, $-NHC(=O)R_x$, $-SO_2R_3$, cyano, hydroxy, alkoxy, substituted amino, or $-C(=O)R_3$ (wherein R_xR_y g, R_6 and R_3 are as defined above);

20

R_4 can be hydrogen; alkyl, hydroxyl, halogen, or carboxy;

WO 2007/045980

PCT/IB2006/002931

- 57 -

R_7 can be hydrogen, or alkyl;

R_1 can be independently hydrogen or alkyl and R_2 and R_4 forms an optionally substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s) selected from the group consisting of N, O and S, wherein the substituents is one or more of oxo, alkyl, $-C(=O)OR_3$, $-SO_2R_3$, halogen, hydroxy, alkoxy, $-NH_2$ or substituted amino (wherein R_3 is as defined below), with the proviso that R_2 and R_4 together does not form $-CH_2-O-CH_2-O-CH_2-$;

X_1 and X_2 can be hydrogen, alkyl, cycloalkyl, alkaryl, alkenyl, cycloalkylalkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclalkyl, $-(CH_2)_gC(=O)NR_xR_y$ or $-(CH_2)_{g_1}C(=O)OR_3$ (wherein g can be an integer from 0-3 and g_1 can be an integer from 1-3, and R_x , R_y and R_3 are as defined below);

X_1 and X_2 together can optionally form a cyclic ring fused with the ring A shown in Formula I, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms N, O or S;

wherein R_3 can be alkyl, cycloalkyl or heterocyclyl;

wherein the halogen can be F, Cl, Br, or I; R_x and R_y each independently can be hydrogen, alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, carboxy, cycloalkyl, $-S(O)_mR_5$, aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclalkyl; m can be an integer between 0-2; R_6 can be alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclalkyl;

wherein R_5 can be hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl;

In another aspect, provided are pharmaceutical compositions comprising one or more phosphodiesterase inhibitors of type IV ("PDE-IV"), and at least one other active ingredients selected from muscarinic receptor antagonists (MRA), β_2 -agonists, p38 MAP Kinase inhibitors, and corticosteroids and one or more pharmaceutically acceptable excipients, wherein the PDE-IV is one or more compounds having the structure of Formula Ia and Formula Ib, as described herein.

WO 2007/045980

PCT/IB2006/002931

- 58 -

The pharmaceutical compositions of each of the above aspects can include, for example, one or more of the following illustrative compounds of Formula Ia or Formula Ib:

- 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-en-6-ol
5 (Compound No. 1),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-*N*-(4-fluorophenyl)-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-carboxamide (Compound No. 2),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-7-(tetrahydrofuran-3-ylcarbonyl)-1-oxa-2,7-diazaspiro[4.4]non-2-ene (Compound No. 3),
- 10 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-*N,N*-dimethyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-sulfonamide (Compound No. 4),
- N*-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-carboxamide (Compound No. 5),
- 2-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-en-7-yl}acetamide (Compound No. 6),
15
- Hydrochloride salt of 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-8-prolyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 7),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-(2-morpholin-4-yl-ethyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 8),
- 20 *N*-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxamide (Compound No. 9),
- 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-8-(methylsulfonyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 10),
- 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.4]non-2-ene (Compound
25 No. 11),
- 3-[3,4-bis(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 12),
- 3-(3,4-diisopropoxyphenyl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 13),

WO 2007/045980

PCT/IB2006/002931

- 59 -

3-[3-methoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 14),

3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-en-8-one
(Compound No. 15),

5 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-en-8-ol
(Compound No. 16).

3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-7-isopropyl-1-oxa-2, 7-diazaspiro [4.4] non-2-ene
(Compound No. 17),

10 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-7-(cyclopropylcarbonyl)-1-oxa-2,7-diazaspiro[4.4]non-2-ene (Compound No. 18),

N-benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-carboxamide (Compound No. 19),

7-acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene
(Compound No. 20),

15 *Tert*-butyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene-7-carboxylate (Compound No. 21),

N-butyl-*N'*-{3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}urea (Compound No. 22),

20 *N*-{3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}-*N'*-(2-methoxyphenyl)urea (Compound No. 23),

3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-ol (Compound No. 24),

Hydrochloride salt of 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene (Compound No. 25),

25 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-one
(Compound No. 26),

3-[3,4-bis(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 27),

WO 2007/045980

PCT/IB2006/002931

- 60 -

- 3-[3,4-Bis(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 28),
- 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-en-4-ol (Compound No. 29),
- 5 (R)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 30),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-(cyclopropylmethyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 31),
- N*-Benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-
10 carboxamide (Compound No. 32),
- 3-[3,4-Bis(benzyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 33),
- 4-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)benzene-1,2-diol (Compound No. 34),
- 7-Amino-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-en-6-one (Compound No. 35),
- 15 Ethyl 8-benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-4-carboxylate (Compound No. 36),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-ene-4-carboxylic acid (Compound No. 37),
- 8-Benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene
20 (Compound No. 38),
- Ethyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-ene-4-carboxylate (Compound No. 39),
- 3-[3-(Difluoromethoxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 40),
- 25 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenol (Compound No. 41)
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-en-6-one (Compound No. 42).

WO 2007/045980

PCT/IB2006/002931

- 61 -

- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,6a-dimethyl-3a*H*-cyclopenta[*d*]isoxazole-4,6(5*H*,6a*H*)-dione (Compound No. 43),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazole (Compound No. 44).
- 5 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one (Compound No. 45),
- Tert*-butyl [(3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl)amino]carbonyl]carbamate (Compound No. 46),
- N*-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}cyclopentanecarboxamide (Compound No. 47),
- 10 8-Acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 48),
- 8-(Cyclopentylcarbonyl)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 49),
- 15 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-(2-piperidin-1-ylethyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 50),
- 3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 51),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1,8-dioxa-2-azaspiro[4.5]dec-2-ene
- 20 (Compound No. 52),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a*H*-cyclopenta[*d*]isoxazole-4,6(5*H*,6a*H*)-dione (Compound No. 53),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-ethyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 54),
- 25 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-vinyl-1-oxa-2-azaspiro[4.5]dec-2-en-8-ol (Compound No. 55),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazole (Compound No. 56),

WO 2007/045980

PCT/IB2006/002931

- 62 -

3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole
(Compound No. 57),

N-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}methanesulfonamide(Compound No. 58),

5 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-methyl-1-oxa-2-azaspiro[4.5]dec-2-en-8-ol
(Compound No. 59),

3-[3-(Allyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 60),

3-[3-(2-Chloroethoxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
10 (Compound No. 61),

2-(Cyclopentyloxy)-4-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenol (Compound
No. 62),

3-(4-Butoxy-3-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 63),

15 3-(3-Isobutoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 64),

3-[3-Butoxy-4-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 65),

3-(3-Butoxy-4-ethoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 66),

20 3-[3-Butoxy-4-(cyclohexyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 67),

3-[3-(Cyclohexylmethoxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 68),

3-[3-(Cyclohexylmethoxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
25 (Compound No. 69),

3-[4-Butoxy-3-(cyclohexylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 70),

3-(4-Isobutoxy-3-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 71),

WO 2007/045980

PCT/IB2006/002931

- 63 -

- 3-(4-Butoxy-3-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 72),
- 3-[4-(Cyclohexylmethoxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 73),
- 5 3-[3-Isopropoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 74),
- 3-[3-(Cyclopropylmethoxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 75),
- 3-[3-(Cyclopropylmethoxy)-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 76),
- 10 3-[4-Butoxy-3-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 77),
- 3-[3-(Cyclopropylmethoxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 78),
- 15 3-(3-Isobutoxy-4-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 79),
- 3-[4-(Cyclopropylmethoxy)-3-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 80),
- 3-[4-(cyclohexyloxy)-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 81)
- 20 3-[4-(Cyclohexylmethoxy)-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 82),
- 3-[4-(Cyclopropylmethoxy)-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 83),
- 25 3-[3-(Cyclopentyloxy)-4-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 84),
- 3-[3-(Cyclopentyloxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 85),

WO 2007/045980

PCT/IB2006/002931

- 64 -

- 3-[3-(Cyclopropylmethoxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 86),
- 3-[4-(Cyclopentyloxy)-3-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 87),
- 5 3-[3-Isopropoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 88),
- 3-(4-Ethoxy-3-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 89),
- 3-[3-(Cyclopentyloxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
10 (Compound No. 90),
- 3-[4-Butoxy-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 91),
- 3-[3-(Cyclopentyloxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 92),
- 15 3-[3-(Cyclopentyloxy)-4-(cycloheptyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 93),
- 3-[3-(Cyclopentyloxy)-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-
2-ene (Compound No. 94),
- 3-[4-(Cyclohexylmethoxy)-3-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
20 (Compound No. 95),
- 3-[4-(Cyclohexylmethoxy)-3-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-
2-ene (Compound No. 96),
- 3-[3-(Cyclopropylmethoxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 97),
- 25 3-[4-(Cyclopentyloxy)-3-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
ene (Compound No. 98),
- 3-[4-(Cyclopropylmethoxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 99),

WO 2007/045980

PCT/IB2006/002931

- 65 -

- 3-[4-(Cyclopentyloxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 100),
- 3-(3-Isopropoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 101),
- 5 3-(4-Ethoxy-3-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 102),
- 3-[3-Butoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 103),
- 3-[3-Butoxy-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
10 No. 104),
- 3-(3-Butoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 105),
- 3-(3-Butoxy-4-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
No. 106),
- 15 3-[3-(Cyclohexylmethoxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 107),
- 3-[3-(Cyclohexylmethoxy)-4-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 108),
- 3-[3-(Cyclohexylmethoxy)-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
20 ene (Compound No. 109),
- 3-[3-(Cyclohexylmethoxy)-4-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-
2-ene (Compound No. 110),
- 3-[4-(Cyclohexylmethoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 111),
- 25 3-[4-(Cyclopropylmethoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 112),
- 3-[4-(Cyclopentyloxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 113),

WO 2007/045980

PCT/IB2006/002931

- 66 -

- 3-[4-(3-Isobutoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 114),
- 3-[3-(Cycloheptyloxy)-4-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 115),
- 5 3-[3-(Cycloheptyloxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 116),
- 3-[4-Butoxy-3-(cycloheptyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 117),
- 3-[3-(Cycloheptyloxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
10 (Compound No. 118),
- 3-[3-(Cycloheptyloxy)-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 119),
- 3-(3-Ethoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 120),
- 3-[4-(Cycloheptyloxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
15 No. 121),
- 3-[4-(Cyclopropylmethoxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 122),
- 3-[4-(Cyclohexylmethoxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 123),
- 20 (S)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 124),
- 3-(3-Butoxy-4-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 125),
- 3-(3-Ethoxy-4-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
25 No. 126),
- 3-[4-(Cyclopentyloxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 127),
- 3-(4-Butoxy-3-ethoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 128),

WO 2007/045980

PCT/IB2006/002931

- 67 -

- 3-(3-Ethoxy-4-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 129),
- 3-[3-(Cycloheptyloxy)-4-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 130),
- 5 3-[3-(Cycloheptyloxy)-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 131),
- 3-[3-(Cycloheptyloxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 132),
- 10 3-(4-Butoxy-3-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 133),
- 3-(4-Ethoxy-3-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 134),
- 3-[4-(Morpholin-4-ylethoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 135),
- 3-(4-Isopropoxy-3-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
- 15 No. 136),
- 2-[5-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]cyclopentanol (Compound No. 137),
- N*-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}-2-fluorobenzamide (Compound No. 138),
- 20 *N*-{3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}benzamide (Compound No. 139).
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]isoxazole (Compound No. 140)
- 7-(Cyclopentylcarbonyl)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene (Compound No. 141),
- 25 *Tert*-butyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-3a,4,6,6a-tetrahydro-5*H*-pyrrolo[3,4-*d*]isoxazole-5-carboxylate (Compound No. 142),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxamide (Compound No. 143),

WO 2007/045980

PCT/IB2006/002931

- 68 -

- N*-Butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene-7-carboxamide (Compound No. 144).
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-7-(methylsulfonyl)-1-oxa-2,7-diazaspiro[4.5]dec-2-ene (Compound No. 145),
- 5 3-[4-Methoxy-3-(pyridin-3-ylmethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 146),
- 5-Acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]isoxazole (Compound No. 147),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-(methylsulfonyl)-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-*d*]isoxazole (Compound No. 148),
- 10 4-Bromo-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 149),
- 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,5,6,7a-tetrahydro-1,2-benzisoxazol-7(4*H*)-one (Compound No. 150).
- 15 3-[4-(Difluoromethoxy)-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 151),
- 3-[4-(Cyclopentyloxy)-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 152),
- 3-[4-Butoxy-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 153),
- 20 3-(3-{[3-(Benzyloxy)cyclopentyl]oxy}-4-methoxyphenyl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 154),
- 7-Acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene (Compound No. 155),
- 25 3-[4-Methoxy-3-(pyridin-2-ylmethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 156),
- 3-[3-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-ethoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 157),

WO 2007/045980

PCT/IB2006/002931

- 69 -

- 3-[3-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 158),
- 3-[4-(Cyclopropylmethoxy)-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 159),
- 5 3-[3-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 160),
- 2-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenol (Compound No. 161),
- N*-cyclopropyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetamide (Compound No. 162),
- 10 Hydrochloride salt of 3-[4-methoxy-3-(piperidin-3-yloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 163),
- 2-[5-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetamide (Compound No. 164),
- 15 Ethyl [5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetate (Compound No. 165),
- [5-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetonitrile (Compound No. 166),
- 3-{3-[(2,6-Dichloropyridin-4-yl)methoxy]-4-methoxyphenyl}-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 167),
- 20 [3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(4-carboxylic acid tert butylester-piperazin-1-yl-carbonyl)-4,5-dihydroisoxazol-5-yl]-({4-carboxylic-acid- tert butyl ester piperazine-1-yl) ethanone (Compound No. 168),
- 1-{1-[5-(4-Acetyl-4-phenyl-piperidine-1-carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazole-5-yl]-4-acetyl-4-phenyl-piperidin-4-yl]-ethanone (Compound No. 169)
- 25 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-pyrrolidin-1-yl-ethanone (Compound No. 170),

WO 2007/045980

PCT/IB2006/002931

- 70 -

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(piperidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-piperidin-1-yl-ethanone (Compound No. 171),

3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(pyrrolidin-2-carboxylic acid methyl ester-1-carbonyl)-4,5-dihydro-isoxazol-5-yl)-[{pyrrolidine-2-carboxylic acid methyl ester-5-yl]
5 ethanone (Compound No. 172),

[5-[4-(4-Chlorophenyl)-4-hydroxy-piperidine-1-carbonyl]-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazol-5-yl]-[4-(4-chlorophenyl)-4-hydroxy-piperidin-1-yl]-ethanone (Compound No. 173)

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(hydroxymethyl-piperidine-1-carbonyl)-4,5-dihydro-isoxazol-5-yl]-(4-hydroxymethyl-piperidin-1-yl)-ethanone (Compound No. 174),
10

[5-(5-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-(carbonyl)-3-(3-cyclopentyloxy-4-methoxy-phenyl)-4,5-dihydro-isoxazol-5-yl]-5-benzyl-2,5-diazabicyclo-[2.2.1]hept-2-yl-ethanone (Compound No. 175),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperidin-1-yl-methanone (Compound No. 176),
15

4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester (Compound No. 177),

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-carbonyl]-pyrrolidin-2-carboxylic acid (Compound No. 178),

20 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-carbonyl]-pyrrolidine-2-carboxylic acid methyl ester (Compound No. 179),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-yl]-pyrrolidin-1-yl-methanone (Compound No. 180),

[1-4]-Bipiperidinyl-1-yl-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 181),
25

1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-4-phenyl-piperidine-4-yl}-ethanone (Compound No. 182),

[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-methyl-piperazin-1-yl)-methanone (Compound No. 183),

WO 2007/045980

PCT/IB2006/002931

- 71 -

- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperazin-1-yl-methanone (Compound No. 184),
- [4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-methanone (Compound No. 185),
- 5 {4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-[1,4]diazepan-1-yl}-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 186),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-cyclopropylmethyl-piperazin-1-yl)-methanone (Compound No. 187),
- 10 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-isobutyl-1-piperazin-1-yl)-methanone (Compound No. 188),
- [3-Hydroxymethyl-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 189),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-hydroxy-piperidin-1-yl)-methanone (Compound No. 190),
- 15 (4-Benzyl-piperidin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 191),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-piperidin-4-one (Compound No. 192),
- 20 [4-(4-Bromophenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 193),
- (5-Benzyl-2,5-diaza-bicyclo [2.2.1] hept-2-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 194),
- (4-Benzyl-piperazin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 195),
- 25 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-pyrrolidin-2-carboxylic acid methyl amide (Compound No. 196),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-pyrrolidine-2-carboxylic acid diethyl amide (Compound No. 197),

WO 2007/045980

PCT/IB2006/002931

- 72 -

- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(2-hydroxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 198),
- 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonyl]-piperidine-2-carboxylic acid methyl ester (Compound No. 199),
- 5 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carboxyl]-pyrrolidine-2-carboxylic acid amide (Compound No. 200),
- 3-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-bicyclo[2.2.1]heptan-2-one (Compound No. 201),
- 3-[3-Cyclopentyloxy-4-methoxy-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-en-6-one
10 (Compound No. 202),
- 3-[3-Cyclopentyloxy-4-methoxy-phenyl]-7-methyl-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-6,9-dione (Compound No. 203),
- [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(2-methoxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 204),
- 15 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene (Compound No. 205),
- 3-(3-Cyclopropylmethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 206),
- 3-(4-Difluoromethoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
20 (Compound No. 207),
- 3-(4-Difluoro-3-butoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 208),
- 3-(4-Difluoromethoxy-3-isobutoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene (Compound No. 209),
- 25 3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 210),
- 3-(3-Benzoyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene (Compound No. 211),

WO 2007/045980

PCT/IB2006/002931

- 73 -

- 3-(4-Difluoromethoxy-3-cyclopentyloxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 212),
- 3-(3,4-Bis-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 213),
- 5 3-(3-Butoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro [4,4] non-2-ene
(Compound No. 214),
- 3-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-difluoromethoxy-phenyl]-1,7-dioxo-2-aza-
spiro[4.4]non-2-ene (Compound No. 215),
- 3-(4-Difluoromethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
10 (Compound No. 216),
- 3-(4-Benzoyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 217),
- 3-(3-Cycloheptyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 218),
- 15 4-(1,7-Dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 219),
- 3-[3-(indan-2-yloxy)-4-methoxy-phenyl]-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
(Compound No. 220),
- 3-(4-Ethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 221),
- 20 3-(3-Methoxy-4-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 222),
- 3-(4-Isopropoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 223),
- 3-(4-Butoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
25 No. 224),
- 3-(4-Cyclopentyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
(Compound No. 225),
- 3-(4-(Isobutoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 226),

WO 2007/045980

PCT/IB2006/002931

- 74 -

- 3-(4-Cyclohexyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
(Compound No. 227),
- 3-(4-Cyclopropylmethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 228),
- 5 3-(3,4-Dimethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 229),
3-(3-Ethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 230),
3-(4-Methoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 231),
- 10 3-(3-Isopropoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 232),
3-(3-Butoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
No. 233),
3-(3-Isobutoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
15 No. 234),
3-[4-Methoxy-3-(3-methyl-butoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 235),
3-(3-Cyclohexyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
(Compound No. 236),
- 20 3-(3-Cycloheptyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
(Compound No. 237),
3-[4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
(Compound No. 238),
3-(3-Benzyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
25 No. 239),
5-(1,7-Dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 240),
3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-
carboxylic acid isopropyl ester (Compound No. 241),

WO 2007/045980

PCT/IB2006/002931

- 75 -

- Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene (Compound No. 242),
- 4-Chloro-N-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carbonyl]-benzene sulfonamide (Compound No. 243),
- 5 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2, 8-diazaspiro [4.5] dec-2-ene-8-carboxylic acid-(2,6-difluoro-phenyl)-amide (Compound No. 244),
- 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylic acid-(2,4-dichloro-phenyl)-amide (Compound No. 245),
- 10 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-carbamic acid isopropyl ester (Compound No. 246),
- Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-ylamine (Compound No. 247),
- 2-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-isoindole-1,3-dione (Compound No. 248),
- 15 7-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-oxa-6-aza-spiro[3.4]oct-6-ene (Compound No. 249),
- 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-ene (Compound No. 250),
- 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-
- 20 carboxylic acid tert-butyl ester (Compound No. 251),
- Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diazaspiro[4.4]non-2-ene (Compound No. 252),
- 3-[3-{{(3*S*)-1-Benzylpyrrolidin-3-yl}oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 253),
- 25 3-[2-(Difluoromethoxy)-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]propan-1-ol (Compound No. 254),
- [2-(Difluoromethoxy)-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetonitrile (Compound No. 255),

WO 2007/045980

PCT/IB2006/002931

- 76 -

4-[(5S or 5R)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound No. 256),

4-[(5R or 5S)-1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound No. 257),

5 5-[(5S or 5R)-1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound No. 258),

(5S or 5R)-3-(3,4-Dimethoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 259),

10 (5R or 5S)-3-(3,4-Dimethoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 260),

2-(Benzyloxy)-4-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenol (Compound No. 261),

2-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]ethanol (Compound No. 262),

15 3-[4-(Difluoromethoxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 263),

3-[3-(Cyclohexyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 264),

(5R or 5S)-3-[4-(Difluoromethoxy)-3-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 265),

20 (5S or 5R)-3-[4-(Difluoromethoxy)-3-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 266),

Ethyl [2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetate (Compound No. 267),

25 3-[4-(Difluoromethoxy)-3-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 268),

2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl cyclohexanecarboxylate (Compound No. 269),

WO 2007/045980

PCT/IB2006/002931

- 77 -

- 5-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]pentanoic acid (Compound No. 270),
- 3-[3-(2,2,2-Trifluoroethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 271),
- 5 3-[3-(Cyclopentylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 272),
- N*-cyclopropyl-2-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetamide (Compound No. 273),
- 2-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetamide
10 (Compound No. 274),
- 2-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]-*N*-methylacetamide (Compound No. 275),
- 3-[3-(Cyclopentylloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 276),
- 15 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl cyclopropanecarboxylate (Compound No. 277),
- 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl morpholine-4-carboxylate (Compound No. 278),
- 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl benzoate
20 (Compound No. 279),
- 5-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy] pentanamide (Compound No. 280),
- 3-[3-Propoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 281),
- 25 3-[3-Isopropoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 282),
- 3-[3-(Cyclopropylmethoxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 283),

WO 2007/045980

PCT/IB2006/002931

- 78 -

3-[3-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 284),

5-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)phenol (Compound No. 285),

5 3-[3-Methoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 286),

3-[3-Ethoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 287),

10 3-[3-Butoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene10019955 (Compound No. 288),

3-[3-(Cyclohexylmethoxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 289),

3-{{2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy}methyl} benzonitrile (Compound No. 290),

15 2-{2-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]ethyl}-1*H*-isoindole-1,3(2*H*)-dione (Compound No. 291),

3-[3-(Cyclohexyloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 292),

20 Ethyl [5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)phenoxy]acetate (Compound No. 293),

3-[3-(Cyclohexylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 294),

Tert-butyl [2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetate (Compound No. 295),

25 *N*-cyclopropyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)phenoxy]acetamide (Compound No. 296),

2-(Cyclopentyloxy)-4-[(5*R* or 5*S*)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol (Compound No. 297),

WO 2007/045980

PCT/IB2006/002931

- 79 -

- 2-(Cyclopentyloxy)-4-[(5S or 5R)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol
(Compound No. 298),
- N-benzyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)
phenoxy]acetamide (Compound No. 299),
- 5 N-Cyclopentyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)
phenoxy]acetamide (Compound No. 300),
- Tert-butyl 4-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]
piperidine-1-carboxylate (Compound No. 301),
- Hydrochloride salt of 3-[4-(difluoromethoxy)-3-(piperidin-4-yloxy)phenyl]-1,7-dioxo-2-
10 azaspiro[4.4]non-2-ene (Compound No. 302),
- 3-{3-[(1-Acetylpiperidin-4-yl)oxy]-4-(difluoromethoxy)phenyl}-1,7-dioxo-2-azaspiro
[4.4]non-2-ene (Compound No. 303),
- Tert-butyl (3S)-3-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-
yl)phenoxy]pyrrolidine-1-carboxylate (Compound No. 304),
- 15 Tert-butyl (3R)-3-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-
yl)phenoxy]pyrrolidine-1-carboxylate (Compound No. 305),
- Tert-butyl 3-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-
yl)phenoxy]piperidine-1-carboxylate (Compound No. 306),
- Tert-butyl (2S)-2-{[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-
20 yl)phenoxy]methyl}pyrrolidine-1-carboxylate (Compound No. 307),
- (5R or 5S)-3-[3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-
azaspiro[4.4]non-2-ene (Compound No. 308),
- (5S or 5R)-3-(3-isopropoxy-4-methoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene
(Compound No. 309),
- 25 (5S or 5R)-3-[3-(Cyclopropylmethoxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-
2-ene (Compound No. 310),
- 2-(Cyclopropylmethoxy)-4-[(5S or 5R)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol
(Compound No. 311),

WO 2007/045980

PCT/IB2006/002931

- 80 -

- 4-[(5S or 5R)-1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl]-2-isopropoxyphenol (Compound No. 312),
- (5S or 5R)-3-[3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 313),
- 5 (5S or 5R)-3-[3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 314),
- (5S or 5R)-3-[4-(difluoromethoxy)-3-isopropoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 315),
- (5R or 5S)-3-[4-(difluoromethoxy)-3-isopropoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 316),
- 10 2-(Cyclopropylmethoxy)-4-[(5R or 5S)-1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl]phenol (Compound No. 317),
- 4-[(5R or 5S)-1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl]-2-isopropoxyphenol (Compound No. 318),
- 15 (5R or 5S)-3-[3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 319), (5R or 5S)-3-[4-(difluoromethoxy)-3-isopropoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 320),
- Hydrochloride salt of 3-{4-(difluoromethoxy)-3-[(3S)-pyrrolidin-3-yloxy]phenyl}-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 321),
- 20 Hydrochloride salt of 3-{4-(difluoromethoxy)-3-[(2S)-pyrrolidin-2-ylmethoxy]phenyl}-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 322),
- Hydrochloride salt of 3-{4-(difluoromethoxy)-3-[(2R)-pyrrolidin-2-ylmethoxy]phenyl}-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 323),
- 3-[4-(Difluoromethoxy)-3-{[(2R)-1-propionylpyrrolidin-2-yl]methoxy}phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 324),
- 25 3-[3-{[(2S)-1-acetylpyrrolidin-2-yl]methoxy}-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 325),
- 3-[3-{[(3S)-1-benzoylpyrrolidin-3-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 326),

WO 2007/045980

PCT/IB2006/002931

- 81 -

- 3-[4-(Difluoromethoxy)-3-{[(3S)-1-propionylpyrrolidin-3-yl]oxy}phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 327),
- (5S or 5R)-3-[3-(Benzyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 328),
- 5 2-(Benzyloxy)-4-[(5S or 5R)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol (Compound No. 329),
- (5S or 5R)-3-[3-(Benzyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 330),
- 10 3-{4-(Difluoromethoxy)-3-[(1-propionylpiperidin-4-yl)oxy]phenyl}-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 331),
- 3-[4-(Difluoromethoxy)-3-{[1-(4-fluorobenzoyl)piperidin-4-yl]oxy}phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 332),
- 3-[3-{[1-(Cyclopropylcarbonyl)piperidin-4-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 333),
- 15 3-[3-{[1-(Cyclopentylcarbonyl)piperidin-4-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 334),
- 3-[4-(Difluoromethoxy)-3-({1-[(trifluoromethyl)sulfonyl]piperidin-4-yl}oxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 335),
- 3-{3-[(1-Acetylpiperidin-3-yl)oxy]-4-(difluoromethoxy)phenyl}-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 336),
- 20 3-{4-(Difluoromethoxy)-3-[(1-propionylpiperidin-3-yl)oxy]phenyl}-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 337),
- 3-[4-(Difluoromethoxy)-3-{[1-(4-fluorobenzoyl)piperidin-3-yl]oxy}phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 338),
- 25 3-[3-{[1-(Cyclopropylcarbonyl)piperidin-3-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 339),
- 3-[3-{[1-(Cyclopentylcarbonyl)piperidin-3-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 340),

WO 2007/045980

PCT/IB2006/002931

- 82 -

3-[4-(Difluoromethoxy)-3-{{1-(ethylsulfonyl)piperidin-3-yl}oxy}phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 341),

3-[3-(Benzyloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 342),

5 2-(Difluoromethoxy)-5-[(5*S* or 5*R*)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol (Compound No. 343), or

5-[(5*R* or 5*S*)-1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound No. 344).

Herein are provided pharmaceutical dosage forms comprising a therapeutically effective amount of one or more compounds of Formula Ia and Formula Ib and one or more pharmaceutically acceptable excipients.

In another aspect, herein are provided pharmaceutical dosage forms comprising a therapeutically effective amount of one or more compounds of Formula Ia or Formula Ib, a therapeutically effective amount of one or more muscarinic receptor antagonists (MRA), and one or more pharmaceutically acceptable excipients. The pharmaceutical dosage form may also include a therapeutically effective amount of one or more corticosteroids, one or more β 2-agonists, one or more p38 MAP kinase inhibitors, one or more anticholinergics, one or more antiallergics, one or more PAF antagonists, one or more leukotriene antagonists, one or more EGFR kinase inhibitors, or one or more additional PDE-IV inhibitors or combinations thereof.

In another aspect, herein are provided pharmaceutical dosage forms comprising a therapeutically effective amount of one or more compounds of Formula Ia or Formula Ib, a therapeutically effective amount of one or more β 2-agonists, and one or more pharmaceutically acceptable excipients. The pharmaceutical dosage form may also include a therapeutically effective amount of one or more corticosteroids, one or more muscarinic receptor antagonists, one or more p38 MAP kinase inhibitors, one or more anticholinergics, one or more antiallergics, one or more PAF antagonists, one or more leukotriene antagonists, one or more EGFR kinase inhibitors, or one or more additional PDE-IV inhibitors or combinations thereof.

In yet another aspect, herein are provided pharmaceutical dosage forms comprising a therapeutically effective amount of one or more compounds of Formula Ia or

WO 2007/045980

PCT/IB2006/002931

- 83 -

Formula Ib, a therapeutically effective amount of one or more p38 MAP kinase inhibitors, and one or more pharmaceutically acceptable excipients. The pharmaceutical dosage form may also include a therapeutically effective amount of one or more β 2-agonists, one or more muscarinic receptor antagonists, one or more corticosteroids, one or more
5 anticholinergics, one or more antiallergics, one or more PAF antagonists, one or more leukotriene antagonists, one or more EGFR kinase inhibitors, or one or more additional PDE-IV inhibitors or combinations thereof.

In still another aspect, herein are provided pharmaceutical dosage forms comprising a therapeutically effective amount of one or more compounds of Formula Ia or
10 Formula Ib, a therapeutically effective amount of one or more corticosteroids, and one or more pharmaceutically acceptable excipients. The pharmaceutical dosage form may also include a therapeutically effective amount of one or more β 2-agonists, one or more muscarinic receptor antagonists, one or more p38 MAP kinase inhibitors, one or more anticholinergics, one or more antiallergics, one or more PAF antagonists, one or more
15 leukotriene antagonists, one or more EGFR kinase inhibitors, or one or more additional PDE-IV inhibitors or combinations thereof.

The β 2-agonists may be chosen from those described in the art or subsequently discovered. The β 2-agonists may include, for example, one or more compounds described in U.S. Patent Nos. 3,705,233; 3,644,353; 3,642,896; 3,700,681; 4,579,985; 3,994,974;
20 3,937,838; 4,419,364; 5,126,375; 5,243,076; 4,992,474; or 4,011,258.

Suitable β 2-agonists include, for example, one or more of albuterol, salbutamol, biltolterol, pirbuterol, levosalbutamol, tulobuterol, terbutaline, bambuterol, metaproterenol, fenoterol, salmeterol, carmoterol, arformoterol, formoterol, and their pharmaceutically acceptable salts or solvates thereof.

Suitable corticosteroids may be chosen from those described in the art. Suitable corticosteroids may include, for example, one or more compounds described in U.S. Patent Nos. 3,312,590; 3,983,233; 3,929,768; 3,721,687; 3,436,389; 3,506,694; 3,639,434;
3,992,534; 3,928,326; 3,980,778; 3,780,177; 3,652,554; 3,947,478; 4,076,708; 4,124,707;
4,158,055; 4,298,604; 4,335,121; 4,081,541; 4,226,862; 4,290,962; 4,587,236; 4,472,392;
30 4,472,393; 4,242,334; 4,014,909; 4,098,803; 4,619,921; 5,482,934; 5,837,699; 5,889,015;

WO 2007/045980

PCT/IB2006/002931

- 84 -

5,278,156; 5,015,746; 5,976,573; 6,337,324; 6,057,307; 6,723,713; 6,127,353; or 6,180,781.

Suitable corticosteroids may include, for example, one or more of alclometasone, amcinonide, amelometasone, beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, cloticasone, cyclomethasone, deflazacort, deprodone, dexamethasone, dexamethasone, diflorasone, difluprednate, fluticasone, flunisolide, halometasone, halopredone, hydrocortisone, hydrocortisone, methylprednisolone, mometasone, prednicarbate, prednisolone, rimexolone, tixocortol, triamcinolone, tolterodine, oxybutynin, ulobetasol, rofleponide, KSR 592, as disclosed in US Patent 4,285,937, ST-126, as disclosed in EP 1344526, dexamethasone and pharmaceutically acceptable salts, solvates thereof. Preferred corticosteroids include, for example, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, and dexamethasone, while budesonide, fluticasone, mometasone, ciclesonide. Examples of possible salts or derivatives include: sodium salts, sulfobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates, or furoates. In some cases, the corticosteroids may also occur in the form of their hydrates.

Suitable muscarinic receptor antagonists (MRA) include substances that directly or indirectly block activation of muscarinic cholinergic receptors. Examples include, but are not limited to, quaternary amines (e.g., tiotropium salts, methantheline, ipratropium, propantheline), tertiary amines (e.g., dicyclomine, scopolamine) and tricyclic amines (e.g., telenzepine). Other suitable muscarinic receptor antagonists include benztropine (commercially available as COGENTIN from Merck), hexahydro-sila-difenidol hydrochloride (HHSID hydrochloride disclosed in Lambrecht *et al.*, *Trends in Pharmacol. Sci.*, 10 (Suppl):60 (1989); (+/-)-3-quinuclidinyl xanthene-9-carboxylate hemioxalate (QNX-hemioxalate; Birdsall *et al.*, *Trends in Pharmacol. Sci.*, 4:459 (1983); telenzepine dihydrochloride (Coruzzi *et al.*, *Arch. Int. Pharmacodyn. Ther.*, 302:232 (1989); and Kawashima *et al.*, *Gen. Pharmacol.*, 21:17 (1990)), and atropine.

Suitable anticholinergics include, for example, ipratropium salts, oxitropium salts, salts of the compounds known from WO 02/32899: tropenol N-methyl-2,2-diphenylpropionate, scopine N-methyl-2,2-diphenylpropionate, scopine N-methyl-2-fluoro-2,2-diphenylacetate and tropenol N-methyl-2-fluoro-2,2-diphenylacetate; as well as salts of the compounds known from WO 02/32898: tropenol N-methyl-3,3',4,4'-

WO 2007/045980

PCT/IB2006/002931

- 85 -

tetrafluorobenzilate, scopine N-methyl-3,3',4,4'-tetrafluorobenzilate, scopine N-methyl-4,4'-dichlorobenzilate, scopine N-methyl-4,4'-difluorobenzilate, tropenol N-methyl-3,3'-difluorobenzilate, scopine N-methyl-3,3'-difluorobenzilate, and tropenol N-ethyl-4,4'-difluorobenzilate, optionally in the form of their hydrates and solvates. By salts are meant those compounds which contain, in addition to the above mentioned cations, as counter-
5 ion, an anion with a single negative charge selected from among the chloride, bromide, and methanesulfonate.

Particular anticholinergics include, for example, tiotropium bromide, ipratropium bromide, oxitropium bromide, tropenol 2,2-diphenylpropionate methobromide, scopine
10 2,2-diphenylpropionate methobromide, scopine 2-fluoro-2,2-diphenylacetate methobromide, tropenol 2-fluoro-2,2-diphenylacetate methobromide, tropenol 3,3',4,4'-tetrafluorobenzilate methobromide, scopine 3,3',4,4'-tetrafluorobenzilate methobromide; scopine 4,4'-dichlorobenzilate methobromide, scopine 4,4'-difluorobenzilate methobromide, tropenol 3,3'-difluorobenzilate methobromide, scopine 3,3'-
15 difluorobenzilate methobromide, and tropenol 4,4'-difluorobenzilate ethylbromide.

Suitable antiallergic agents include, for example, epinastine, cetirizine, azelastine, fexofenadine, levocabastine, loratadine, mizolastine, ketotifene, emedastine, dimetindene, clemastine, bamipine, hexachloropheniramine, pheniramine, doxylamine, chlorphenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastine,
20 desloratadine, and meclizine. Particular antiallergic agents include, for example, epinastine, cetirizine, azelastine, fexofenadine, levocabastine, loratadine, ebastine, desloratadine, and mizolastine, epinastine. Any reference to the above-mentioned antiallergic agents also includes any pharmacologically acceptable acid addition salts thereof, which may exist.

25 Suitable PAF antagonists include, for example, 4-(2-chlorophenyl)-9-methyl-2-[3-(4-morpholinyl)-3-propanon-1-yl]-6H-thieno[3,2-f][1,2,4]triazolo[4,3- α][1,4]diazepine and 6-(2-chlorophenyl)-8,9-dihydro-1-methyl-8-[(4-morpholinyl)carbonyl]-4H,7H-cyclopenta[4.5]thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine.

Suitable EGFR kinase inhibitors include, for example, 4-[(3-chloro-4-fluorophenyl)amino]-7-(2-{4-[(S)-(2-oxotetrahydrofuran-5-yl)carbonyl]piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[4-((S)-6-methyl-2-oxomorpholin-4-yl)butyloxy]-6-[(vinylcarbonyl)amino]quinazoline, 4-

30

WO 2007/045980

PCT/IB2006/002931

- 86 -

[(3-chloro-4-fluorophenyl)amino]-7-[4-((R)-6-methyl-2-oxomorpholin-4-yl)butyloxy]-6-
[(vinylcarbonyl)amino]quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[2-((S)-6-
methyl-2-oxomorpholin-4-yl)ethoxy]-6-[(vinylcarbonyl)amino]quinazoline, 4-[(3-chloro-
4-fluorophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)ethyl]-N-[(ethoxycarbonyl)methyl]-
5 amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline, 4-[(R)-(1-
phenylethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropyl-
methoxyquinazoline, and 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-
yl)propyloxy]-7-methoxyquinazoline. Any reference to the above-mentioned EGFR kinase
inhibitors also includes any pharmacologically acceptable acid addition salts thereof which
10 may exist. By the physiologically or pharmacologically acceptable acid addition salts
thereof which may be formed by the EGFR kinase inhibitors are meant, according to the
invention, pharmaceutically acceptable salts selected from among the salts of hydrochloric
acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, acetic acid,
fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, or maleic acid. The salts of
15 the EGFR kinase inhibitors selected from among the salts of acetic acid, hydrochloric acid,
hydrobromic acid, sulfuric acid, phosphoric acid, and methanesulfonic acid are preferred
according to the invention.

Suitable additional PDE-IV inhibitors include, for example, enprofylline,
roflumilast, ariflo, Bay-198004, CP-325,366, BY343, D-4396 (Sch-351591), V-11294A,
20 Z-15370, and AWD-12-281. Particular PDE-IV inhibitors include enprofylline,
roflumilast, ariflo, Z15370, and AWD-12-281. Any reference to the abovementioned
PDE-IV inhibitors also includes any pharmacologically acceptable acid addition salts
thereof which may exist. By the physiologically acceptable acid addition salts which may
be formed by the abovementioned PDE-IV inhibitors are meant, according to the
25 invention, pharmaceutically acceptable salts selected from among the salts of hydrochloric
acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, acetic acid,
fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, or maleic acid. According
to the invention, the salts selected from among the acetate, hydrochloride, hydrobromide,
sulfate, phosphate, and methanesulfonate are preferred in this context.

30 The leukotriene antagonist can be selected from compounds not limited to those
described in US 5,565,473, US 5,583,152, US 4,859,692 or US 4,780,469.

WO 2007/045980

PCT/IB2006/002931

- 87 -

Examples of leukotriene antagonist include, but are not limited to, montelukast, zafirlukast, pranlukast and pharmaceutically acceptable salts thereof.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like.

Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-dibenzylethylenediamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and tromethamine.

When a compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids, such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, nitric, pantothenic, phosphoric, succinic, sulfuric, tartaric, and p-toluenesulfonic acid.

Pharmaceutical compositions of the present invention may be administered by following routes, for example, oral, topical, intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, subcutaneous, intranasally, inhalation, rectally or vaginally.

Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, suppositories, troches, patches, gel caps, magmas, lozenges, creams, pastes, plasters, lotions, discs, or ointments. Liquid form preparations include solutions suspensions, emulsions, syrups, elixirs, aerosols, inhalations, nasal sprays or oral sprays.

WO 2007/045980

PCT/IB2006/002931

- 88 -

The active compound can be admixed under sterile condition with pharmaceutically acceptable carrier and any needed preservatives or buffer as may be required.

Pharmaceutical compositions for use in the methods described herein may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with pharmaceutically acceptable liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

Commonly used carriers include one or more of corn starch, lactose, talc, calcium phosphate, calcium sulphate, calcium stearate, magnesium stearate, stearic acid, sorbitol, microcrystalline cellulose, mannitol, gelatin, natural or synthetic gums, such as carboxymethylcellulose, methylcellulose, alginate, dextran, acacia gum, karaya gum, locust bean gum. Additionally, other excipients such as diluents, binders, lubricants, disintegrants, colors and flavoring agents may be employed. For example, a tablet may be prepared by compression or molding, optionally with one or more pharmaceutically acceptable excipient. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

In addition to the common dosage forms set out above, the therapeutically active ingredients may also be administered by controlled release means and/or delivery devices to provide the rate-controlled release of any one or more of the components or active ingredients to optimize the desired therapeutic effects. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

WO 2007/045980

PCT/IB2006/002931

- 89 -

The "polymeric matrix" serves essentially to modulate drug release kinetics and to stabilize metastable drug. Due to their versatility, polymers represent election material for matrix delivery systems. Indeed polymeric matrices can be profitably used in, for example, oral delivery, implantable systems, tissue engineering, DNA/RNA release, intelligent
5 delivery systems and polymer conjugation.

The magnitude of a prophylactic or therapeutic dose of one or more compounds described herein in the acute or chronic prevention, treatment, or management of a disorder or condition will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to
10 the age, body weight, and response of the individual patient. Suitable total daily dose ranges can be readily determined by those skilled in the art. In general, the total daily dose range for one or more compounds described herein, for the conditions described herein, may range from about 1 mg to about several grams administered in single or divided doses according to the particular application and the potency of the active ingredient. Suitable
15 dosage amounts can be determined using small dosages that are less than the optimum dose. Such small dosages can be increased in small increments until the optimum effect is reached. Dosage amounts may be divided and administered as divided doses if desired.

Phosphodiesterase inhibitors of type IV of Formula Ia and Formula Ib and muscarinic receptor antagonists (MRA) can be present in compositions described herein in
20 ratios from about 1:10 to 10:1. Phosphodiesterase inhibitors of type IV and muscarinic receptor antagonists (MRA) can also be present in compositions described herein in ratios of about 1:1, 2:1, 1:2, 1:3, 3:1, 1:5 and even 5:1.

Phosphodiesterase inhibitors of type IV of Formula Ia and Formula Ib and β 2-agonists can be present in ratios from about 1:10 to 10:1. Phosphodiesterase inhibitors of
25 type IV and β 2-agonists can also be present in compositions described herein in ratios of about 1:1, 2:1, 1:2, 1:3, 3:1, 1:5 and even 5:1.

Phosphodiesterase inhibitors of type IV of Formula Ia and Formula Ib and p38 MAP Kinase inhibitors can be present in compositions described herein in ratios from about 1:10 to 10:1. Phosphodiesterase inhibitors of type IV and p38 MAP Kinase
30 inhibitors can also be present in compositions described herein in ratios of about 1:1, 2:1, 1:2, 1:3, 3:1, 1:5 and even 5:1.

WO 2007/045980

PCT/IB2006/002931

- 90 -

Phosphodiesterase inhibitors of type IV of Formula Ia and Formula Ib and corticosteroids can be present in compositions described herein in ratios from about 1:10 to 10:1. Phosphodiesterase inhibitors of type IV and corticosteroids can also be present in compositions described herein in ratios of about 1:1, 2:1, 1:2, 1:3, 3:1, 1:5 and even 5:1.

5 The present invention also provides for methods of treating or preventing autoimmune, inflammatory, or allergic disorders. Methods include administering to a mammal in need thereof a pharmaceutical dosage form comprising a therapeutically effective amount of one or more compounds described herein of Formula Ia or Formula Ib, and therapeutically effective amount of at least one other active ingredient such as one or
10 more muscarinic receptor antagonists (MRA), β 2-agonists, one or more corticosteroids, or one or more p38 MAP kinase inhibitors, and one or more pharmaceutically acceptable excipients.

 The present invention also provides for methods of treating or preventing autoimmune, inflammatory, or allergic disorders. Methods include administering to a
15 mammal in need thereof a pharmaceutical dosage form comprising a therapeutically effective amount of one or more compounds described herein, of Formula Ia or Formula Ib and therapeutically effective amount of at least one other active ingredient such as one or more anticholinergics, one or more muscarinic receptor antagonists, one or more
antiallergics, one or more PAF antagonists, one or more leukotriene antagonists, one or
20 more EGFR kinase inhibitors, or one or more additional PDE-IV inhibitors, and one or more pharmaceutically acceptable excipients.

 Yet other methods include concurrent or sequential administration to a mammal in need thereof: a) a pharmaceutical dosage form comprising a therapeutically effective amount of one or more compounds described herein of Formula Ia or Formula Ib, and one
25 or more pharmaceutically acceptable excipients; and b) one or more dosage forms comprising therapeutically effective amounts at least one other active ingredient such as one or more of corticosteroids, one or more β 2-agonists, or one or more p38 MAP kinase inhibitors, and one or more pharmaceutically acceptable excipients.

 Yet other methods include concurrent or sequential administration to a mammal in
30 need thereof: a) a pharmaceutical dosage form comprising a therapeutically effective amount of one or more compounds described herein of Formula Ia or Formula Ib, and one

WO 2007/045980

PCT/IB2006/002931

- 91 -

or more pharmaceutically acceptable excipients; and b) one or more dosage forms comprising therapeutically effective amounts at least one other active ingredient such as one or more muscarinic receptor antagonists, one or more anticholinergics, one or more antiallergics, one or more PAF antagonists, one or more leukotriene antagonists, one or
5 more EGFR kinase inhibitors or one or more additional PDE-IV inhibitors, and one or more pharmaceutically acceptable excipients.

In one embodiment, there are provided methods for treating or preventing autoimmune and/or inflammatory/allergic diseases or disorders comprising administering one or more compounds of pharmaceutical compositions described herein. Such
10 autoimmune and/or inflammatory/allergic diseases or disorders include, for example, respiratory disorder, asthma, chronic bronchitis, chronic obstructive pulmonary disease, whooping cough, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, eczema, inflammatory bowel disease, endotoxic shock, anaphylactic shock, laminitis in horses, septic shock, ulcerative colitis, Crohn's disease,
15 reperfusion injury of the myocardium and brain, inflammatory arthritis, periodontitis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, transplant rejection, rhinitis, pruritus, diabetes insipidus, eye diseases, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, orthrosclerosis, atherosclerosis, neurogenic
20 inflammation, pain, cough, rheumatoid arthritis, osteoporosis, osteoarthritis, inflammation, ankylosing spondylitis, transplant rejection, graft versus host disease, hypersecretion of gastric acid, bacterial, fungal induced sepsis, viral induced sepsis, fungal induced septic shock, viral induced septic shock, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle
25 wasting, depression memory impairment, tumor growth, cancerous invasion of normal tissues Hashimoto's thyroiditis (underactive thyroid), Graves' disease (overactive thyroid), Lupus and acquired immuno deficiency syndrome.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the
30 art and are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

WO 2007/045980

PCT/IB2006/002931

- 92 -

Biological Assay Methods:

Example 1: *In-vitro* assay to evaluate efficacy of PDE IV inhibitors in combination with p38 MAP Kinase inhibitors

Cell based Assay for TNF- α release:

- 5 Blood was collected in heparin or EDTA vacutainers from healthy human volunteers and Peripheral Blood Mononuclear Cells isolated using Ficoll Hypaque gradient. The cells were resuspended in serum free RPMI 1640 medium at a concentration of 2 million cells/ml.). 1 ml of this cell suspension was co-incubated with 20 μ l of compound, alone or in combination, for 10 min in a flat bottom 96 well microtiter plate.
- 10 Compounds were dissolved in DMSO initially and diluted in medium for a final concentration of 0.2 % DMSO. LPS (1 μ g/ml, final concentration) was then added at a volume of 10 μ l per well. After 30 min, 20 μ l of fetal calf serum (final concentration of 10 %) was added to each well. Cultures were incubated overnight at 37 °C in an atmosphere of 5 % CO₂ and 95 % air. Supernatant were then removed and tested by ELISA for TNF- α
- 15 release using a commercial kit (e.g. BD Biosciences). The level of TNF- α in treated wells was compared with the vehicle treated controls and inhibitory potency of compound was expressed as IC₅₀ values calculated from the percent inhibition values by using Graph pad prism.

Percent TNF- α drug treated

20 Percent inhibition = $100 - \frac{\text{Percent TNF-}\alpha \text{ drug treated}}{\text{Percent TNF-}\alpha \text{ in vehicle treated}} \times 100$

Percent TNF- α in vehicle treatedIC₅₀ of TNF- α release inhibition:

- Compound No. 266 (PDE IV inhibitor) and p38 MAP Kinase inhibitors (Compound No. 44a, Compound No. 46a, Compound No. 47a and Vx-745, as disclosed in
- 25 WO 98/27098) exhibits following IC₅₀ in inhibiting TNF- α release from human PBMCs.

TABLE 1

Compound	IC ₅₀ (nM)
Compound No. 266	76
Compound No. 44a	3
Compound No. 46a	2
Compound No. 47a	22
Vx-745, as disclosed in WO 98/27098	14

5

10

Compound No. 266 (PDE IV inhibitor) and p38 MAP Kinase inhibitors (Compound No. 44a, Compound No. 46a, Compound No. 47a and Vx-745, as disclosed in WO 98/27098) exhibits following combination index (CI) in inhibiting TNF- α release from human PBMCs.

TABLE 2

Compound	Combination Index (CI)	Indication
Compound No. 266 + Vx-745, as disclosed in WO 98/27098	0.34	Synergy
Compound No. 266 + Compound No. 44a	0.25	Synergy
Compound No. 266 + Compound No. 46a	0.62	Synergy
Compound No. 266 + Compound No. 47a	0.16	Synergy

15

PDE 4 inhibitor Compound No. 266 inhibited the release of TNF alpha with an IC₅₀ value of 76 nM. It exhibited a synergistic response with p38 MAP Kinase inhibitors Compound No. 44a, Compound No. 46a, Compound No. 47a and Vx-745, as disclosed in WO 98/27098 in inhibiting the TNF alpha release in human PBMCs.

WO 2007/045980

PCT/IB2006/002931

- 94 -

Example 2: *In-vitro* assay to evaluate efficacy of PDE IV inhibitors in combination with β 2-agonist - Measurement of Intracellular cAMP Elevation in U937 Cells

U937 cells are grown (human promonocytic cell line) in endotoxin-free RPMI 1640 + HEPES medium containing 10% (v/v) heat-inactivated foetal bovine serum and 1% (v/v) of an antibiotic solution (5000 IU/ml penicillin, 5000 μ g/ml streptomycin). Cells are resuspended ($0.25 \times 10^6/200 \mu$ l) in Krebs' buffer solution and are incubated at 37°C for 15 min in the presence of test compounds or vehicle (20 μ l). Generation of cAMP is initiated by adding 50 μ l of 10 μ M prostaglandin (PGE₂). The reaction is stopped after 15 min, by adding 1 N HCl (50 μ l) and is placed on ice for 30 min. The sample is centrifuged (450g, 3 min), and levels of cAMP are measured in the supernatant by using cAMP enzyme-linked immunosorbent assay kit (Assay Designs). Percent inhibition is calculated by the following formula and IC₅₀ value is calculated with these values using Graph pad prism.

Percent conversion in drug treated

Percent inhibition = $100 - \frac{\text{Percent conversion in drug treated}}{\text{Percent conversion in vehicle treated}} \times 100$

Percent conversion in vehicle treated

Example 3: *In-vitro* functional assays to evaluate efficacy of PDE IV inhibitors in combination with beta-agonists

Animals and anaesthesia

Guinea Pig is procured (400-600gm) and trachea is removed under anaesthesia (sodium pentobarbital, 300 mg/kg i.p) and is immediately kept in ice-cold Krebs Henseleit buffer. Indomethacin (10 μ M) is present throughout the KH buffer to prevent the formation of bronchoactive prostanoids.

Trachea experiments:

The tissue of adherent fascia is cleaned and cut into strips of equal size (with approx. 4-5 tracheal rings in each strip). Epithilium is carefully removed by rubbing, minimizing damage to the smooth muscle. The trachea is opened along the mid-dorsal surface with the smooth muscle band intact and a series of transverse cuts is made from alternate sides so that they do not transect the preparation completely. Opposite end of the cut rings is tied with the help of a thread. The tissue is mounted in isolated tissue baths containing 10ml

WO 2007/045980

PCT/IB2006/002931

- 95 -

Krebs Henseleit buffer maintained at 37°C and bubbled with carbogen, at a basal tension of 1 gm. The buffer is changed 4-5 times for about an hour. The tissue is equilibrated for 1 hr with 1 µM carbachol or 10 µM histamine for stabilization. The tissue is washed for 30 minutes followed by a precontraction with histamine (10 µM) or carbachol (1 µM). The tension which is developed is allowed to stabilize for 15-20 minutes followed by the cumulative addition of beta-agonists prior to incubation with suboptimal dose of PDE IV inhibitor. The contractile response of tissues is recorded either on Powerlab data acquisition system or on Grass polygraph (Model 7). The relaxation as percentage is expressed of maximum carbachol response. The data is expressed as mean ± S.E. mean for n observations. The EC₅₀ is calculated as the concentration producing 50% of the maximum relaxation to 1 µM carbachol. The percent relaxation is compared between the treated and control tissues using non-parametric unpaired t-test. A p value of < 0.05 is considered to be statistically significant.

Example 4: *In-vivo* assay to evaluate efficacy of PDE IV inhibitors in combination with beta-agonists

Lipopolysaccharide (LPS) induced airway hyperreactivity (AHR) and neutrophilia:

Drug treatment:

Beta-agonist (1 ng/kg to 1 mg/kg) and PDE4 inhibitor (1 ng/kg to 1 mg/kg) are instilled intratracheally under anesthesia either alone or in combination.

Method:

Male wistar rats weighing 200±20 gm are used in the study. Rats should have free access to food and water. On the day of experiment, animals are exposed to lipopolysaccharide (LPS, 100 µg/ml) for 40 min. One group of vehicle treated rats should be exposed to phosphate buffered saline (PBS) for 40 min. Two hours after LPS/PBS exposure, animals are placed inside a whole body plethysmograph (Buxco Electronics, USA) and are exposed to PBS or increasing acetylcholine (1, 6, 12, 24, 48 and 96 mg/ml) aerosol until Penh values (index of airway resistance) of rats attain 2 times the value (PC-100) seen with PBS alone. Respiratory parameters are recorded online using Biosystem XA software, (Buxco Electronics, USA). Penh, at any chosen dose of acetylcholine is expressed as percent of PBS response and PC100 (2 folds of PBS value) values computed

using a nonlinear regression analysis. Percent inhibition is computed using the following formula.

5

$$\% \text{ Inhibition} = \frac{\text{PC100}_{\text{LPS}} - \text{PC100}_{\text{TEST}}}{\text{PC100}_{\text{LPS}} - \text{PC100}_{\text{PBS}}} \times 100$$

Where,

$\text{PC100}_{\text{LPS}}$ = PC100 in vehicle treated group challenged group with LPS

$\text{PC100}_{\text{TEST}}$ = PC100 in group treated with a given dose of test compound

$\text{PC100}_{\text{PBS}}$ = PC100 in vehicle treated group challenged with PBS

10 Immediately after the airway hyperreactivity response is recorded, animals are
ethanized and bronchoalveolar lavage (BAL) is performed. Collected lavage fluid is
centrifuged at 3000 rpm for 5 min, at 4°C. Pellet is collected and resuspend in 1ml HBSS.
Total leukocyte count is determined in the resuspended sample. A portion of suspension to
be cytocentrifuged and stained with Leishmann's stain for differential leukocyte count.
15 Total leukocyte and Neutrophil counts are expressed as cell count (millions cells ml⁻¹ of
BAL). Percent inhibition I computed using the following formula.

$$\% \text{ Inhibition} = \frac{\text{NC}_{\text{LPS}} - \text{NC}_{\text{TEST}}}{\text{NC}_{\text{LPS}} - \text{NC}_{\text{PBS}}} \times 100$$

20 Where,

NC_{LPS} = Percentage of neutrophil in vehicle treated group challenged with LPS

NC_{TEST} =Percentage of neutrophil in group treated with a given dose of test compound

NC_{PBS} = Percentage of neutrophil in vehicle treated group challenged with PBS

ED₅₀ vales are computed from the percent inhibition data using Graph Pad Prism software
25 (Graphpad Software Inc.,USA).

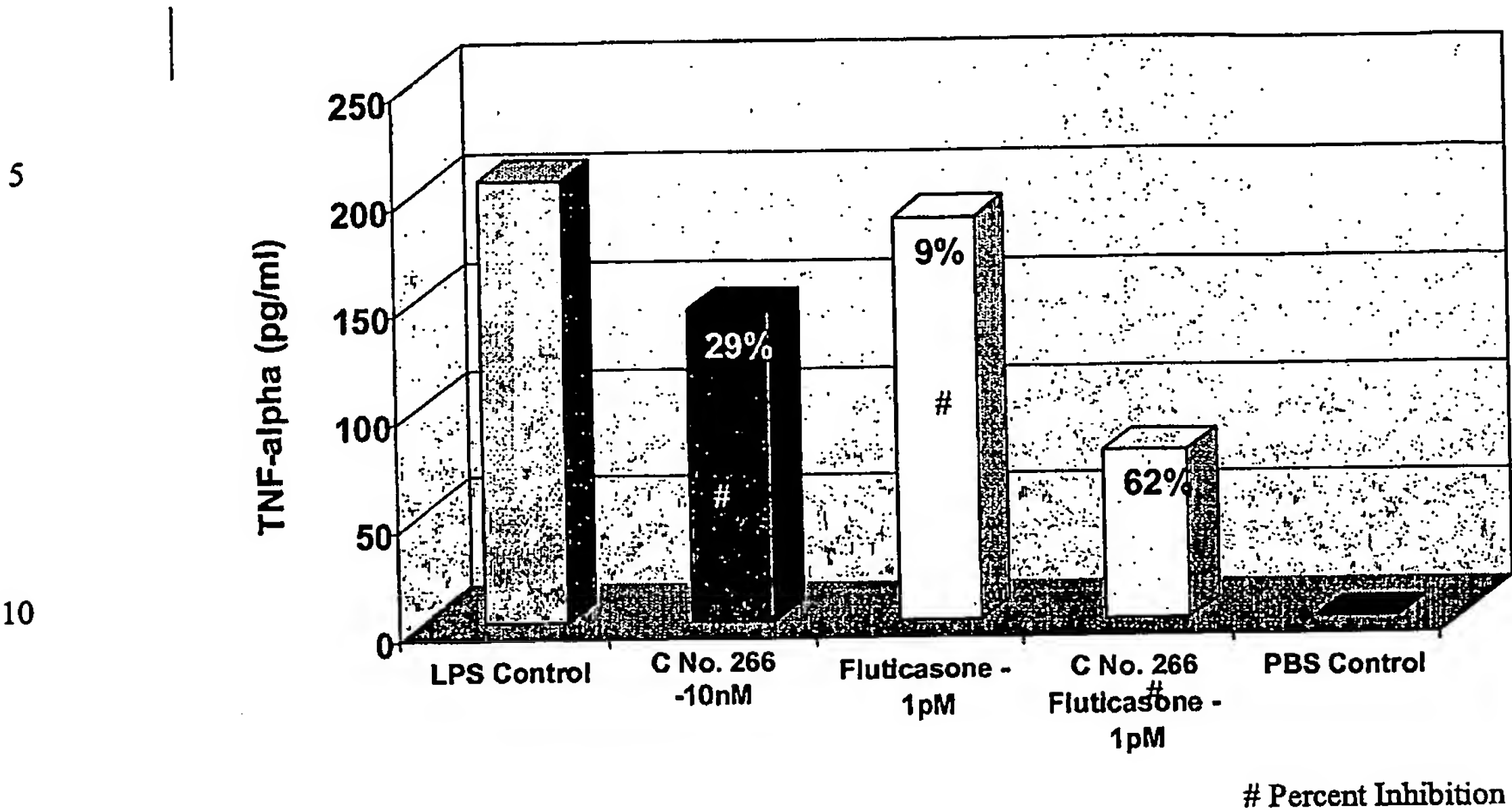
Example 5: *In-vitro* assay to evaluate efficacy of PDE IV inhibitors in combination with corticosteroids

Cell based Assay for TNF- α release:

Blood was collected in heparin or EDTA vacutainers from healthy human
5 volunteers and. Peripheral Blood Mononuclear Cells isolated using Ficoll Hypaque
gradient. The cells were resuspended in serum free RPMI 1640 medium at a concentration
of 2 million cells/ml). 1 ml of this cell suspension was co-incubated with 20 μ l of
compound, alone or in combination (PDE IV inhibitor and corticosteroid), for 10 min in a
flat bottom 96 well microtiter plate The aforesaid compounds were dissolved in DMSO
10 initially and diluted in medium for a final concentration of 0.2 % DMSO. LPS (1 mg/ml,
final concentration) was then added at a volume of 10 μ l per well. After 30 min, 20 μ l of
fetal calf serum (final concentration of 10 %) was added to each well. Cultures were
incubated overnight at 37 $^{\circ}$ C in an atmosphere of 5 % CO₂ and 95 % air. Supernatant was
then removed and tested by ELISA for TNF- α release using a commercial kit (e.g. BD
15 Biosciences). The level of TNF- α in treated wells was compared with the vehicle treated
controls and inhibitory potency of compound was expressed as IC₅₀ values calculated by
from percent inhibition values using Graph pad prism. IC₅₀ values of test compounds are
found to be in the range of lower μ M to nM concentration.

$$\begin{array}{l} \text{Percent TNF-}\alpha \text{ drug treated} \\ 20 \quad \text{Percent inhibition} = 100 - \frac{\text{Percent TNF-}\alpha \text{ drug treated}}{\text{Percent TNF-}\alpha \text{ in vehicle treated}} \times 100 \end{array}$$

A synergistic effect was observed with the combination of PDE IV inhibitor with corticosteroid which can be seen from below mentioned graphs.



- C No. 266 refers to Compound No. 266
- Combination Index=0.21 indicating synergistic activity
- C No. 266 showed synergy with corticosteroids indicating potential to lower dose

Example 6: *In-vivo* assay to evaluate efficacy of PDE IV inhibitors in combination with corticosteroids

LPS induced rat neutrophilia model

Drug treatment:

PDE-4 inhibitor and corticosteroids were instilled intratracheally under anesthesia at different doses, either alone or in combination

LPS challenge: One hour after drug instillation, (LPS 20 µg/200 µl of PBS) was instilled intratracheally. One group of vehicle treated rats were instilled with 200 µl of phosphate buffered saline (PBS) and served as negative control.

Bronchoalveolar lavage (BAL): Two hours after LPS challenge, bronchoalveolar lavage was performed; the animals were sacrificed using thiopentone sodium (150 mg/kg/i.p.).

WO 2007/045980

PCT/IB2006/002931

- 99 -

Trachea was cannulated and BAL was performed using Hank's Buffer salt solution (HBSS) (5 ml x 10 times). The bronchoalveolar lavage fluid was centrifuged at 800 g for 5 min, at 4°C and the pellet was resuspended in 1 ml HBSS. Total leukocyte count was performed in the resuspended sample by using hemocytometer. A cytocentrifuge
5 preparation was made using the resuspended bronchoalveolar lavage fluid on a glass slide, stained with Leishmann's stain and then differential leukocyte counts was performed for computation of neutrophil. Statistical significance of each parameter in different treatment groups was determined with respect to vehicle control group using one-way analysis of variance followed by Dunnett's 't' test for multiple comparison. A p level of ≤0.05 was
10 considered to be statistically significant.

Percent inhibition was computed using the following formula.

$$\% \text{ Inhibition} = \frac{\text{Neu}_{\text{LPS}} - \text{Neu}_{\text{TEST}}}{\text{Neu}_{\text{LPS}} - \text{Neu}_{\text{PBS}}} \times 100$$

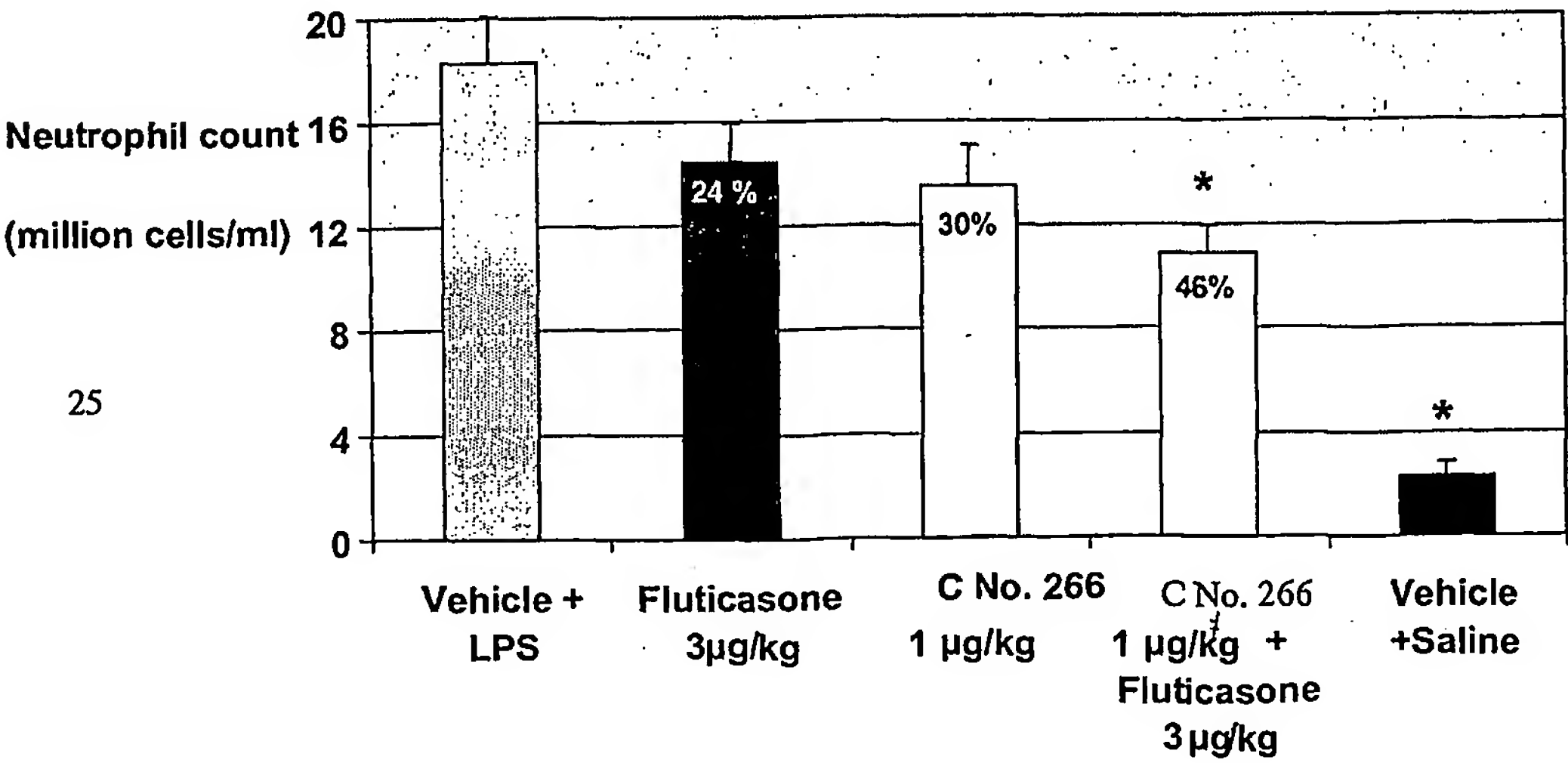
15 Where,

Neu_{LPS} = Neutrophil count in vehicle treated LPS challenged group

Neu_{TEST} = Neutrophil count in group treated with a given dose of test compound

Neu_{PBS} = Percentage of Neutrophil in group challenged with PBS

A synergistic effect was seen with the combination of PDE IV inhibitor with
20 corticosteroids which is apparent from the graph given below:



#Percent inhibition values

- C No. 266 refers to Compound No. 266.
- Combination Index = 0.58 indicating synergistic activity
- C No. 266 (PDE IV inhibitor) showed synergy with corticosteroids indicating a potential to lower dose

Example 7: *In-vivo* assay to evaluate efficacy of PDE-IV inhibitors in combination with Muscarinic Receptor Antagonists (MRA)

Drug treatment:

MRA (1ng/kg to 1mg/kg) and PDE-IV inhibitor (1ng/kg to 1mg/kg) were instilled intratracheally under anesthesia either alone or in combination.

Method:

Wistar rats weighing 200±20gm were used in the study. Rats had free access to food and water. On the day of experiment, animals were exposed to lipopolysaccharide (LPS, 100µg/ml) for 40 min. One group of vehicle treated rats was exposed to phosphate buffered saline (PBS) for 40 min. Two hours after LPS/PBS exposure, animals were placed inside a whole body plethysmograph (Buxco Electronics, USA) and exposed to PBS or increasing concentration of acetylcholine (1, 6, 12, 24, 48 and 96 mg/ml) aerosol until Penh values (index of airway resistance) of rats attained 2 times the value (PC-100) seen with PBS alone. The respiratory parameters were recorded online using Biosystem XA software, (Buxco Electronics, USA). Penh, at any chosen dose of acetylcholine was expressed as percent of PBS response and using a nonlinear regression analysis PC100 (2 folds of PBS value) values were computed. Percent inhibition was computed using the following formula.

$$\% \text{ Inhibition} = \frac{\text{PC100}_{\text{LPS}} - \text{PC100}_{\text{TEST}}}{\text{PC100}_{\text{LPS}} - \text{PC100}_{\text{PBS}}} \times 100$$

Where,

PC100_{LPS} = PC100 in vehicle treated and LPS challenged group

WO 2007/045980

PCT/IB2006/002931

- 101 -

PC100_{TEST} = PC100 in group treated with a given dose of test compound

PC100_{PBS} = PC100 in vehicle treated group challenged with PBS

Immediately after the airway hyperreactivity response was recorded, animals were sacrificed and bronchoalveolar lavage (BAL) performed. Collected lavage fluid was centrifuged at 3000 rpm for 5 min, at 4°C. Pellet was collected and resuspended in 1ml HBSS. Total leukocyte count was performed in the resuspended sample. A portion of suspension was cytocentrifuged and stained with Leishmann's stain for differential leukocyte count. Total leukocyte and Neutrophil counts were expressed as cell count (millions cells ml⁻¹ of BAL). Percent inhibition was computed using the following formula.

$$\% \text{ Inhibition} = \frac{NC_{LPS} - NC_{TEST}}{NC_{LPS} - NC_{PBS}} \times 100$$

Where,

NC_{LPS} = Percentage of neutrophil in vehicle treated group challenged with LPS

NC_{TEST} = Percentage of neutrophil in group treated with a given dose of test compound

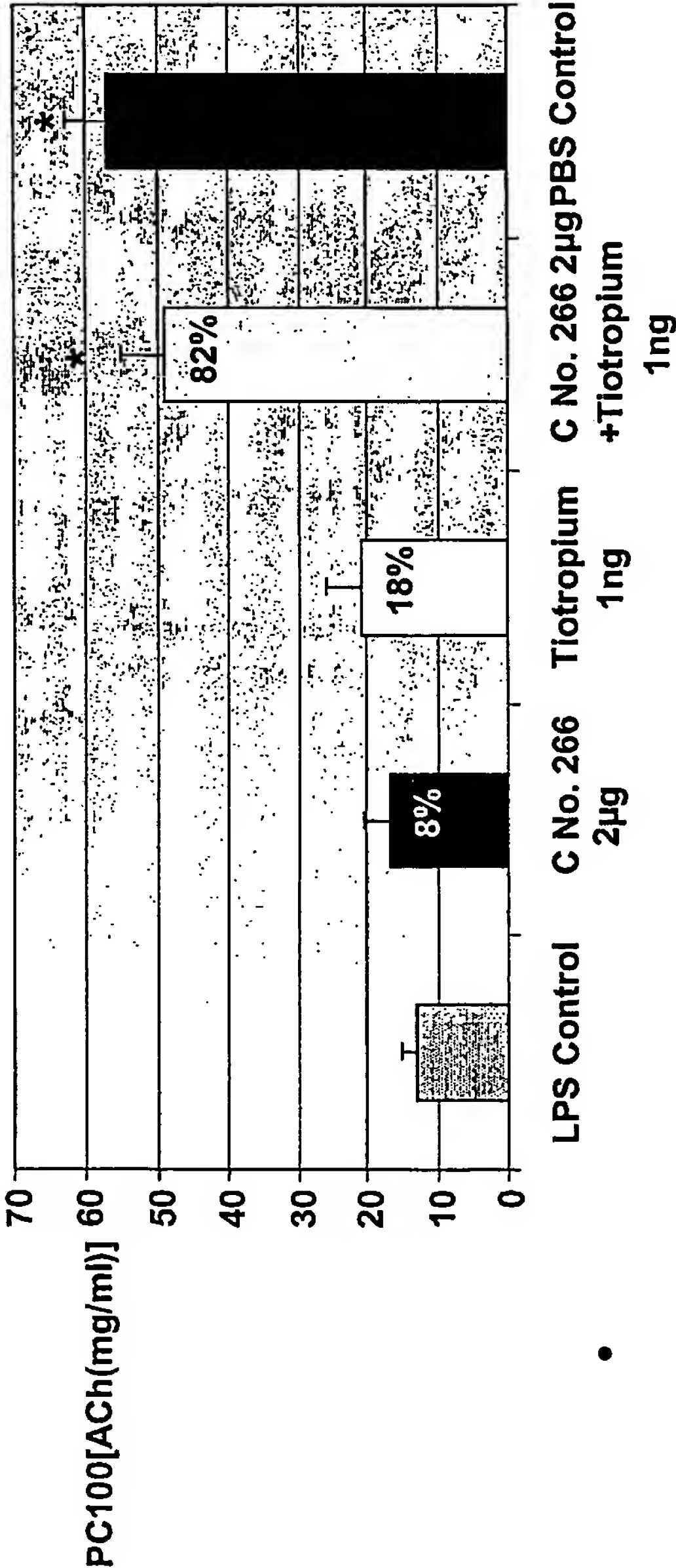
NC_{PBS} = Percentage of neutrophil in vehicle treated group challenged with PBS

WO 2007/045980

PCT/IB2006/002931

- 102 -

A synergistic effect was observed with the combination of muscarinic receptor antagonist (MRA) with PDE 4 inhibitor which can be seen from below mentioned graph.



• C No. 266 (PDE IV inhibitor) showed synergy with Tiotropium (MRA) indicating a potential to lower dose

WO 2007/045980

PCT/IB2006/002931

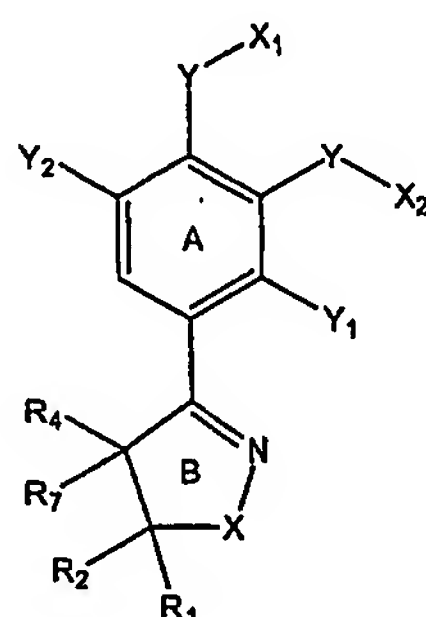
- 103 -

We claim:

1. A pharmaceutical composition comprising one or more phosphodiesterase inhibitors of type IV ("PDE-IV"), and at least one other active ingredients selected from muscarinic receptor antagonists (MRA), β 2-agonists, p38 MAP Kinase inhibitors, and corticosteroids and one or more pharmaceutically acceptable excipients wherein the PDE-IV is one or more compounds having the structure of Formula Ia or Formula Ib

wherein

a. Formula Ia is:



FORMULA Ia

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides, wherein

When X is oxygen,

- R₁** is hydrogen, alkyl, heterocyclyl, $-(CH_2)_mC(=O)R_3$, or $(CH_2)_{1-4}OR'$, (wherein m is an integer 0-2, R₃ is alkyl, cycloalkyl, heterocyclyl, or optionally substituted R_p or R_q, wherein R_p is heterocyclyl or heteroaryl ring, wherein the rings are attached to $(CH_2)_mC(=O)$ through N, and R_q is heterocyclyl or heteroaryl ring wherein the rings are attached to $-(CH_2)_mC(=O)$ through C, and wherein R' is alkyl, alkenyl, alkynyl, saturated or unsaturated cycloalkyl, aryl, heterocyclyl or heteroaryl);
- R₂** is $(CH_2)_mC(=O)R_3$, $-(CH_2)_{1-4}OR'$, or $C(=O)NR_xR_y$ {where m, R₃ and R' are as defined above, and wherein R_x and R_y each independently is hydrogen, alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, cycloalkyl, carboxy, $-S(O)_mR_5$ (wherein R₅ is hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl,

WO 2007/045980

PCT/IB2006/002931

- 104 -

heterocyclyl or heterocyclalkyl), aryl, alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclalkyl}, or R_1 and R_2 together form an optionally substituted cycloalkyl or heterocycl ring wherein the optional substituent is oxo, alkyl, alkenyl, alkynyl, halogen, nitro, $-NH_2$, $-NHC(=O)OR_6$, $-C(=O)NR_xR_y$, cyano, hydroxy, alkoxy, or substituted amino (wherein R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclalkyl), with the proviso that if R_1 is $-(CH_2)_{1-4}OR'$, then R_2 is also $-(CH_2)_{1-4}OR'$, and with the proviso that if R_1 is $C(=O)NR_xR_y$, then R_2 is also $C(=O)NR_xR_y$;

R_4 is hydrogen; alkyl; $-OR_5$; halogen; $-NH_2$, substituted amino; cyano; carboxy; or $-C(=O)NR_xR_y$ (wherein R_5 , R_x and R_y are as defined above); or R_2 and R_4 forms an optionally substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system fused to ring B having 0-4 heteroatom(s), wherein the substituents are one or more of alkyl, halogen, hydroxy, alkoxy, $-NH_2$ or substituted amino (wherein R_3 and R_x and R_y are as defined above), with the proviso that R_2 and R_4 together does not form $-CH_2-O-CH_2-O-CH_2-$;

R_7 is hydrogen, alkyl, alkenyl, alkynyl, $-OR_5$, halogen, cyano, $-NH_2$, or substituted amino;

X_1 and X_2 each independently is hydrogen, alkyl, alkaryl, cycloalkyl, alkaryl, alkenyl, cycloalkylalkyl, heterocyclyl, heteroaryl, heterocyclalkyl, $-(CH_2)_gC(=O)NR_xR_y$, $-(CH_2)_{g1}C(=O)OR_3$ or heteroarylalkyl; wherein g_1 is an integer from 1-3 (wherein R_x , R_y , g and R_3 are as defined above);

Y is each independently an oxygen atom; a sulphur atom; or $-NR$ (wherein R is hydrogen, acyl, aryl, or alkyl);

Y_1 and Y_2 each independently is hydrogen; alkyl; $-OR$; $-SR$; or $-NHR$ (wherein R is as defined above);

wherein any of Y_1 and X_2 & X_1 and Y_2 together optionally form a ring fused with the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3 heteroatoms, and X_1 and X_2 can together optionally form a ring fused with ring A, the ring containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms, and

WO 2007/045980

PCT/IB2006/002931

- 105 -

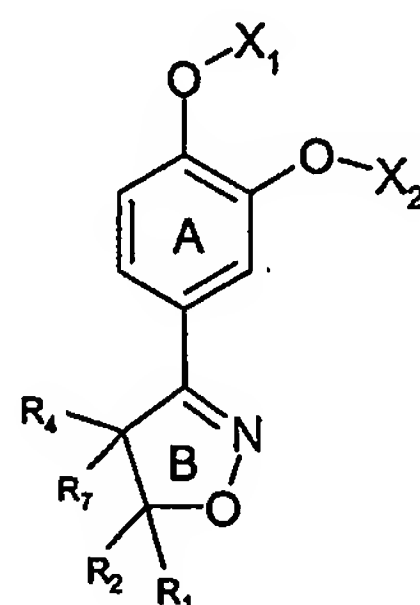
- 55 When X is NR₇, or S (wherein R₇ can be hydrogen, or C₁₋₆ alkyl)
- 56 R₁ and R₂ is independently alkyl, alkenyl, alkynyl, alkoxy, hydroxy, cyano, nitro,
 57 halogen, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclalkyl, NH₂,
 58 substituted amino, carboxy, -(CH₂)_mC(=O)R₃, -C(=O)NR_xR_y, or (CH₂)₁₋₄OR',
 59 {wherein m is an integer 0-2, R₃ is alkyl, cycloalkyl, heterocyclyl, or optionally
 60 substituted R_p or R_q (wherein R_p is heterocyclyl or heteroaryl ring, wherein the
 61 rings are attached to (CH₂)_mC(=O) through N, and R_q is heterocyclyl or heteroaryl
 62 ring wherein the rings are attached to -(CH₂)_mC(=O) through C), wherein R' is
 63 alkyl, alkenyl, alkynyl, saturated or unsaturated cycloalkyl, aryl, heterocyclyl or
 64 heteroaryl, and wherein R_x and R_y each independently is hydrogen, alkyl, C₃-C₆
 65 alkenyl, C₃-C₆ alkynyl, cycloalkyl, carboxy, -S(O)_mR₅ (wherein R₅ is hydrogen,
 66 alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl, heteroarylalkyl,
 67 heterocyclyl or heterocyclalkyl), aryl, alkaryl, heteroaryl, heterocyclyl,
 68 heteroarylalkyl, or heterocyclalkyl}, or R₁ and R₂ together form an optionally
 69 substituted cycloalkyl or heterocyclyl ring wherein the optional substituent is oxo,
 70 alkyl, alkenyl, alkynyl, halogen, nitro, -NH₂, -NHC(=O)OR₆ (wherein R₆ is alkyl,
 71 alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl or heterocyclalkyl), -
 72 C(=O)NR_xR_y, cyano, hydroxy, alkoxy, or substituted amino;
- 73 R₄ is hydrogen; alkyl; -OR₅; halogen; -NH₂, substituted amino; cyano; carboxy; or -
 74 C(=O)NR_xR_y (wherein R₅, R_x and R_y are as defined above); or R₂ and R₄ forms an
 75 optionally substituted 4-12 membered saturated or unsaturated monocyclic or
 76 bicyclic ring system fused to ring B having 0-4 heteroatom(s), wherein the
 77 substituents can be one or more of alkyl, halogen, hydroxy, alkoxy or substituted
 78 amino (wherein R₃ and R_x and R_y are as defined above), with the proviso that R₂
 79 and R₄ together does not form -CH₂-O-CH₂-O-CH₂-;
- 80 R₇ is hydrogen, alkyl, alkenyl, alkynyl, -OR₅, halogen, cyano, -NH₂, or substituted
 81 amino;
- 82 X₁ and X₂ each independently is alkyl, cycloalkyl, alkaryl, heteroaryl, heterocyclyl,
 83 heteroarylalkyl, or heterocyclalkyl;

WO 2007/045980

PCT/IB2006/002931

- 106 -

- 84 **Y** is each independently an oxygen atom; a sulphur atom; or -NR (wherein R is
85 hydrogen, acyl, aryl, or alkyl);
- 86 **Y₁** and **Y₂** each independently is hydrogen, alkyl, -OR, -SR, or -NHR (wherein R is as
87 defined above);
- 88 wherein any of **Y₁** and **X₂** & **X₁** and **Y₂** together optionally form a ring fused with
89 the ring A, the ring containing 3-5 carbon atoms within the ring and having 1-3
90 heteroatoms such as N, O and S;
- 91 **X₁** and **X₂** can together optionally form a cyclic ring fused with the ring A, the ring
92 containing 3-5 carbon atoms within the ring and having 2-3 heteroatoms,
- 93 and
- 94 b. Formula Ib is:



Formula Ib

- 95
- 96 and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates,
97 enantiomers, diastereomers or N-oxides, wherein
- 98 **R₁** and **R₂** together forms an optionally substituted cycloalkyl or heterocyclyl ring
99 wherein one or more optional substituent are oxo, alkyl, alkaryl, alkenyl, alkynes,
100 heterocyclylalkyl, cycloalkylalkyl, -SO₂NR_xR_y, halogen, -NH₂, -(CH₂)_gC(=O)NR_xR_y, -
101 NHC(=O)OR₆, -NHC(=O)NR_xR_y, -C(=O)OR₃, -NHC(=O)R_x, -SO₂R₃, cyano, hydroxy,
102 alkoxy, substituted amino, or -C(=O)R₃ (wherein R_xR_y g, R₆ and R₃ are as defined above);
- 103 **R₄** is hydrogen; alkyl, hydroxyl, halogen, or carboxy;
- 104 **R₇** is hydrogen, or alkyl;
- 105 **R₁** is independently hydrogen or alkyl and **R₂** and **R₄** forms an optionally
106 substituted 4-12 membered saturated or unsaturated monocyclic or bicyclic ring system

WO 2007/045980

PCT/IB2006/002931

- 107 -

107 fused to ring B having 0-4 heteroatom(s), wherein the substituents is one or more of oxo,
108 alkyl, -C(=O)OR₃, -SO₂R₃, halogen, hydroxy, alkoxy, -NH₂ or substituted amino (wherein
109 R₃ is as defined below), with the proviso that R₂ and R₄ together does not form -CH₂-O-
110 CH₂-O-CH₂-;

111 X₁ and X₂ are hydrogen, alkyl, cycloalkyl, alkaryl, alkenyl, cycloalkylalkyl,
112 heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclalkyl, -(CH₂)_gC(=O)NR_xR_y or -
113 (CH₂)_{g1}C(=O)OR₃ (wherein g can be an integer from 0-3 and g₁ can be an integer from
114 1-3, and R_x, R_y and R₃ are as defined below);

115 X₁ and X₂ together can optionally form a cyclic ring fused with the ring A shown
116 in Formula I, the ring containing 3-5 carbon atoms within the ring and having 2-3
117 heteroatoms N, O or S;

118 wherein R₃ is alkyl, cycloalkyl or heterocyclyl;

119 wherein the halogen can be F, Cl, Br, or I; R_x and R_y each independently can be
120 hydrogen, alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, carboxy, cycloalkyl, -S(O)_mR₅, aryl,
121 alkaryl, heteroaryl, heterocyclyl, heteroarylalkyl, and heterocyclalkyl; m can be an
122 integer between 0-2; R₆ can be alkyl, alkenyl, alkynyl, cycloalkyl, alkaryl, heteroarylalkyl
123 or heterocyclalkyl; and

124 wherein R₅ is hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkaryl, heteroaryl,
125 heteroarylalkyl, heterocyclyl or heterocyclalkyl.

1 2. The pharmaceutical composition of claim 1, wherein the one or more
2 compounds of Formula Ia or Formula Ib are selected from:

3 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-en-6-ol
4 (Compound No. 1),

5 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-N-(4-fluorophenyl)-1-oxa-2,7-
6 diazaspiro[4.4]non-2-ene-7-carboxamide (Compound No. 2),

7 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-7-(tetrahydrofuran-3-ylcarbonyl)-1-oxa-2,7-
8 diazaspiro[4.4]non-2-ene (Compound No. 3),

9 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-N,N-dimethyl-1-oxa-2,7-diazaspiro[4.4]non-2-
10 ene-7-sulfonamide (Compound No. 4),

WO 2007/045980

PCT/IB2006/002931

- 108 -

- 11 *N*-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-
- 12 carboxamide (Compound No. 5),
- 13 2-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-en-7-
- 14 yl}acetamide (Compound No. 6),
- 15 Hydrochloride salt of 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-8-prolyl-1-oxa-2,8-
- 16 diazaspiro[4.5]dec-2-ene (Compound No. 7),
- 17 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-(2-morpholin-4-yl-ethyl)-1-oxa-2,8-
- 18 diazaspiro[4.5]dec-2-ene (Compound No. 8),
- 19 *N*-butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-
- 20 carboxamide (Compound No. 9),
- 21 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-8-(methylsulfonyl)-1-oxa-2,8-
- 22 diazaspiro[4.5]dec-2-ene (Compound No. 10),
- 23 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.4]non-2-ene (Compound No.
- 24 11),
- 25 3-[3,4-bis(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
- 26 (Compound No. 12),
- 27 3-(3,4-diisopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 13),
- 28 3-[3-methoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
- 29 (Compound No. 14),
- 30 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-en-8-one
- 31 (Compound No. 15),
- 32 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-en-8-ol
- 33 (Compound No. 16).
- 34 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-7-isopropyl-1-oxa-2, 7-diazaspiro [4.4] non-2-
- 35 ene (Compound No. 17),
- 36 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-7-(cyclopropylcarbonyl)-1-oxa-2,7-
- 37 diazaspiro[4.4]non-2-ene (Compound No. 18),
- 38 *N*-benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-
- 39 carboxamide (Compound No. 19),

WO 2007/045980

PCT/IB2006/002931

- 109 -

- 40 7-acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene
41 (Compound No. 20),
- 42 *Tert*-butyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene-
43 7-carboxylate (Compound No. 21),
- 44 *N*-butyl-*N'*-{3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-
45 yl}urea (Compound No. 22),
- 46 *N*-{3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}-*N'*-(2-
47 methoxyphenyl)urea (Compound No. 23),
- 48 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-ol (Compound
49 No. 24),
- 50 Hydrochloride salt of 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-
51 diazaspiro[4.5]dec-2-ene (Compound No. 25),
- 52 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-one
53 (Compound No. 26),
- 54 3-[3,4-bis(cyclopentyloxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No.
55 27),
- 56 3-[3,4-Bis(cyclopropylmethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound
57 No. 28),
- 58 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-en-4-ol
59 (Compound No. 29),
- 60 (R)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene
61 (Compound No. 30),
- 62 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-(cyclopropylmethyl)-1-oxa-2,8-
63 diazaspiro[4.5]dec-2-ene (Compound No. 31),
- 64 *N*-Benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-
65 carboxamide (Compound No. 32),
- 66 3-[3,4-Bis(benzyloxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 33),
- 67 4-(1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl)benzene-1,2-diol (Compound No. 34),

WO 2007/045980

PCT/IB2006/002931

- 110 -

- 68 7-Amino-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-en-6-
69 one (Compound No. 35),
- 70 Ethyl 8-benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-
71 ene-4-carboxylate (Compound No. 36),
- 72 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-ene-4-carboxylic
73 acid (Compound No. 37),
- 74 8-Benzyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene
75 (Compound No. 38),
- 76 Ethyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-ene-4-
77 carboxylate (Compound No. 39),
- 78 3-[3-(Difluoromethoxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene
79 (Compound No. 40),
- 80 2-(Difluoromethoxy)-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)phenol (Compound No.
81 41)
- 82 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.4]non-2-en-6-one
83 (Compound No. 42).
- 84 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,6a-dimethyl-3a*H*-cyclopenta[*d*]isoxazole-
85 4,6(5*H*,6a*H*)-dione (Compound No. 43),
- 86 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazole
87 (Compound No. 44).
- 88 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one
89 (Compound No. 45),
- 90 *Tert*-butyl [(3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-
91 yl)amino]carbonyl]carbamate (Compound No. 46),
- 92 *N*-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-
93 yl}cyclopentanecarboxamide (Compound No. 47),
- 94 8-Acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene
95 (Compound No. 48),

WO 2007/045980

PCT/IB2006/002931

- 111 -

- 96 8-(Cyclopentylcarbonyl)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-
- 97 diazaspiro[4.5]dec-2-ene (Compound No. 49),
- 98 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-(2-piperidin-1-ylethyl)-1-oxa-2,8-
- 99 diazaspiro[4.5]dec-2-ene (Compound No. 50),
- 100 3-(2,3-Dihydro-1,4-benzodioxin-6-yl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound
- 101 No. 51),
- 102 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1,8-dioxa-2-azaspiro[4.5]dec-2-ene
- 103 (Compound No. 52),
- 104 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a*H*-cyclopenta[*d*]isoxazole-4,6(5*H*,6a*H*)-dione
- 105 (Compound No. 53),
- 106 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-ethyl-1-oxa-2,8-diazaspiro[4.5]dec-2-ene
- 107 (Compound No. 54),
- 108 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-vinyl-1-oxa-2-azaspiro[4.5]dec-2-en-8-ol
- 109 (Compound No. 55),
- 110 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxazole
- 111 (Compound No. 56),
- 112 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole
- 113 (Compound No. 57),
- 114 *N*-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-
- 115 yl}methanesulfonamide(Compound No. 58),
- 116 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-8-methyl-1-oxa-2-azaspiro[4.5]dec-2-en-8-ol
- 117 (Compound No. 59),
- 118 3-[3-(Allyloxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No.
- 119 60),
- 120 3-[3-(2-Chloroethoxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene
- 121 (Compound No. 61),
- 122 2-(Cyclopentyloxy)-4-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)phenol (Compound
- 123 No. 62),

WO 2007/045980

PCT/IB2006/002931

- 112 -

- 124 3-(4-Butoxy-3-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
125 No. 63),
- 126 3-(3-Isobutoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
127 No. 64),
- 128 3-[3-Butoxy-4-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
129 (Compound No. 65),
- 130 3-(3-Butoxy-4-ethoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 66),
131 3-[3-Butoxy-4-(cyclohexyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
132 No. 67),
- 133 3-[3-(Cyclohexylmethoxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
134 (Compound No. 68),
- 135 3-[3-(Cyclohexylmethoxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
136 (Compound No. 69),
- 137 3-[4-Butoxy-3-(cyclohexylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
138 (Compound No. 70),
- 139 3-(4-Isobutoxy-3-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
140 No. 71),
- 141 3-(4-Butoxy-3-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
142 No. 72),
- 143 3-[4-(Cyclohexylmethoxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
144 (Compound No. 73),
- 145 3-[3-Isopropoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
146 (Compound No. 74),
- 147 3-[3-(Cyclopropylmethoxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
148 (Compound No. 75),
- 149 3-[3-(Cyclopropylmethoxy)-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-
150 azaspiro[4.4]non-2-ene (Compound No. 76),
- 151 3-[4-Butoxy-3-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
152 (Compound No. 77),

WO 2007/045980

PCT/IB2006/002931

- 113 -

- 153 3-[3-(Cyclopropylmethoxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
154 (Compound No. 78),
- 155 3-(3-Isobutoxy-4-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
156 No. 79),
- 157 3-[4-(Cyclopropylmethoxy)-3-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
158 (Compound No. 80),
- 159 3-[4-(cyclohexyloxy)-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
160 (Compound No. 81)
- 161 3-[4-(Cyclohexylmethoxy)-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
162 ene (Compound No. 82),
- 163 3-[4-(Cyclopropylmethoxy)-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
164 ene (Compound No. 83),
- 165 3-[3-(Cyclopentyloxy)-4-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
166 (Compound No. 84),
- 167 3-[3-(Cyclopentyloxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
168 No. 85),
- 169 3-[3-(Cyclopropylmethoxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
170 (Compound No. 86),
- 171 3-[4-(Cyclopentyloxy)-3-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
172 (Compound No. 87),
- 173 3-[3-Isopropoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
174 (Compound No. 88),
- 175 3-(4-Ethoxy-3-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
176 No. 89),
- 177 3-[3-(Cyclopentyloxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
178 (Compound No. 90),
- 179 3-[4-Butoxy-3-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
180 No. 91),

WO 2007/045980

PCT/IB2006/002931

- 114 -

- 181 3-[3-(Cyclopentyloxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
- 182 (Compound No. 92),
- 183 3-[3-(Cyclopentyloxy)-4-(cycloheptyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
- 184 (Compound No. 93),
- 185 3-[3-(Cyclopentyloxy)-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-
- 186 2-ene (Compound No. 94),
- 187 3-[4-(Cyclohexylmethoxy)-3-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
- 188 (Compound No. 95),
- 189 3-[4-(Cyclohexylmethoxy)-3-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-
- 190 2-ene (Compound No. 96),
- 191 3-[3-(Cyclopropylmethoxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
- 192 (Compound No. 97),
- 193 3-[4-(Cyclopentyloxy)-3-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
- 194 ene (Compound No. 98),
- 195 3-[4-(Cyclopropylmethoxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
- 196 (Compound No. 99),
- 197 3-[4-(Cyclopentyloxy)-3-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
- 198 (Compound No. 100),
- 199 3-(3-Isopropoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
- 200 No. 101),
- 201 3-(4-Ethoxy-3-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
- 202 No. 102),
- 203 3-[3-Butoxy-4-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
- 204 (Compound No. 103),
- 205 3-[3-Butoxy-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
- 206 No. 104),
- 207 3-(3-Butoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
- 208 No. 105),

WO 2007/045980

PCT/IB2006/002931

- 115 -

- 209 3-(3-Butoxy-4-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
210 No. 106),
- 211 3-[3-(Cyclohexylmethoxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
212 (Compound No. 107),
- 213 3-[3-(Cyclohexylmethoxy)-4-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
214 (Compound No. 108),
- 215 3-[3-(Cyclohexylmethoxy)-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
216 ene (Compound No. 109),
- 217 3-[3-(Cyclohexylmethoxy)-4-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-
218 2-ene (Compound No. 110),
- 219 3-[4-(Cyclohexylmethoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
220 (Compound No. 111),
- 221 3-[4-(Cyclopropylmethoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
222 (Compound No. 112),
- 223 3-[4-(Cyclopentyloxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
224 (Compound No. 113),
- 225 3-[4-(3-Isobutoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No.
226 114),
- 227 3-[3-(Cycloheptyloxy)-4-(cyclopropylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
228 ene (Compound No. 115),
- 229 3-[3-(Cycloheptyloxy)-4-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
230 No. 116),
- 231 3-[4-Butoxy-3-(cycloheptyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
232 No. 117),
- 233 3-[3-(Cycloheptyloxy)-4-isopropoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
234 (Compound No. 118),
- 235 3-[3-(Cycloheptyloxy)-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
236 (Compound No. 119),
- 237 3-(3-Ethoxy-4-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 120),

WO 2007/045980

PCT/IB2006/002931

- 116 -

- 238 3-[4-(Cycloheptyloxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
239 No. 121),
- 240 3-[4-(Cyclopropylmethoxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
241 (Compound No. 122),
- 242 3-[4-(Cyclohexylmethoxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
243 (Compound No. 123),
- 244 (S)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
245 (Compound No. 124),
- 246 3-(3-Butoxy-4-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
247 No. 125),
- 248 3-(3-Ethoxy-4-isopropoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
249 No. 126),
- 250 3-[4-(Cyclopentyloxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
251 No. 127),
- 252 3-(4-Butoxy-3-ethoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 128),
- 253 3-(3-Ethoxy-4-isobutoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
254 No. 129),
- 255 3-[3-(Cycloheptyloxy)-4-isobutoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
256 (Compound No. 130),
- 257 3-[3-(Cycloheptyloxy)-4-(cyclopentyloxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
258 (Compound No. 131),
- 259 3-[3-(Cycloheptyloxy)-4-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
260 No. 132),
- 261 3-(4-Butoxy-3-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
262 No. 133),
- 263 3-(4-Ethoxy-3-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound No. 134),
- 264 3-[4-(Morpholin-4-ylethoxy)-3-propoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
265 (Compound No. 135),

WO 2007/045980

PCT/IB2006/002931

- 117 -

- 266 3-(4-Isopropoxy-3-propoxyphenyl)-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
267 No. 136),
- 268 2-[5-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]cyclopentanol
269 (Compound No. 137),
- 270 *N*-{3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-yl}-2-
271 fluorobenzamide (Compound No. 138),
- 272 *N*-{3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2-azaspiro[4.5]dec-2-en-8-
273 yl}benzamide (Compound No. 139).
- 274 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-
275 *d*]isoxazole (Compound No. 140)
- 276 7-(Cyclopentylcarbonyl)-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-
277 diazaspiro[4.5]dec-2-ene (Compound No. 141),
- 278 *Tert*-butyl 3-[3-(cyclopentyloxy)-4-methoxyphenyl]-3a,4,6,6a-tetrahydro-5*H*-pyrrolo[3,4-
279 *d*]isoxazole-5-carboxylate (Compound No. 142),
- 280 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-
281 carboxamide (Compound No. 143),
- 282 *N*-Butyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene-7-
283 carboxamide (Compound No. 144).
- 284 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-7-(methylsulfonyl)-1-oxa-2,7-
285 diazaspiro[4.5]dec-2-ene (Compound No. 145),
- 286 3-[4-Methoxy-3-(pyridin-3-ylmethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
287 (Compound No. 146),
- 288 5-Acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-4,5,6,6a-tetrahydro-3a*H*-pyrrolo[3,4-
289 *d*]isoxazole (Compound No. 147),
- 290 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-5-(methylsulfonyl)-4,5,6,6a-tetrahydro-3a*H*-
291 pyrrolo[3,4-*d*]isoxazole (Compound No. 148),
- 292 4-Bromo-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
293 (Compound No. 149),

WO 2007/045980

PCT/IB2006/002931

- 118 -

- 294 3-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3a,5,6,7a-tetrahydro-1,2-benzisoxazol-7(4H)-
295 one (Compound No. 150).
- 296 3-[4-(Difluoromethoxy)-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxa-2-
297 azaspiro[4.4]non-2-ene (Compound No. 151),
- 298 3-[4-(Cyclopentyloxy)-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxa-2-
299 azaspiro[4.4]non-2-ene (Compound No. 152),
- 300 3-[4-Butoxy-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-
301 ene (Compound No. 153),
- 302 3-(3-{[3-(Benzyloxy)cyclopentyl]oxy}-4-methoxyphenyl)-1,7-dioxa-2-azaspiro[4.4]non-
303 2-ene (Compound No. 154),
- 304 7-Acetyl-3-[3-(cyclopentyloxy)-4-methoxyphenyl]-1-oxa-2,7-diazaspiro[4.5]dec-2-ene
305 (Compound No. 155),
- 306 3-[4-Methoxy-3-(pyridin-2-ylmethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene
307 (Compound No. 156),
- 308 3-[3-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-ethoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-
309 ene (Compound No. 157),
- 310 3-[3-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-propoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-
311 ene (Compound No. 158),
- 312 3-[4-(Cyclopropylmethoxy)-3-(2,3-dihydro-1*H*-inden-2-yloxy)phenyl]-1,7-dioxa-2-
313 azaspiro[4.4]non-2-ene (Compound No. 159),
- 314 3-[3-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-isopropoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-
315 2-ene (Compound No. 160),
- 316 2-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)phenol
317 (Compound No. 161),
- 318 *N*-cyclopropyl-2-[5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-2-
319 methoxyphenoxy]acetamide (Compound No. 162),
- 320 Hydrochloride salt of 3-[4-methoxy-3-(piperidin-3-yloxy)phenyl]-1,7-dioxa-2-
321 azaspiro[4.4]non-2-ene (Compound No. 163),

WO 2007/045980

PCT/IB2006/002931

- 119 -

- 322 2-[5-(1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetamide
323 (Compound No. 164),
- 324 Ethyl [5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetate (Compound
325 No. 165),
- 326 [5-(1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl)-2-methoxyphenoxy]acetonitrile (Compound
327 No. 166),
- 328 3-{3-[(2,6-Dichloropyridin-4-yl)methoxy]-4-methoxyphenyl}-1,7-dioxa-2-
329 azaspiro[4.4]non-2-ene (Compound No. 167),
- 330 [3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(4-carboxylic acid tert butylester-piperazin-1-
331 yl-carbonyl)-4,5-dihydroisoxazol-5-yl]-({4-carboxylic-acid- tert butyl ester piperazine-1-
332 yl) ethanone (Compound No. 168),
- 333 1-{1-[5-(4-Acetyl-4-phenyl-piperidine-1-carbonyl)-3-(3-cyclopentyloxy-4-methoxy-
334 phenyl)-4,5-dihydro-isoxazole-5-yl]-4-acetyl-4-phenyl-piperidin-4-yl]-ethanone
335 (Compound No. 169)
- 336 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(pyrrolidine-1-carbonyl)-4,5-dihydro-
337 isoxazol-5-yl]-pyrrolidin-1-yl-ethanone (Compound No. 170),
- 338 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(piperidine-1-carbonyl)-4,5-dihydro-isoxazol-
339 5-yl]-piperidin-1-yl-ethanone (Compound No. 171),
- 340 3-(3-Cyclopentyloxy-4-methoxy phenyl)-5-(pyrrolidin-2-carboxylic acid methyl ester-1-
341 carbonyl)-4,5-dihydro-isoxazol-5-yl)-[{pyrrolidine-2-carboxylic acid methyl ester-5-yl]
342 ethanone (Compound No. 172),
- 343 [5-[4-(4-Chlorophenyl)-4-hydroxy-piperidine-1-carbonyl]-3-(3-cyclopentyloxy-4-
344 methoxy-phenyl)-4,5-dihydro-isoxazol-5-yl]-[4-(4-chlorophenyl)-4-hydroxy-piperidin-1-
345 yl]-ethanone (Compound No. 173)
- 346 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-(hydroxymethyl-piperidine-1-carbonyl)-4,5-
347 dihydro-isoxazol-5-yl]-(4-hydroxymethyl-piperidin-1-yl)-ethanone (Compound No. 174),
- 348 [5-(5-Benzyl-2,5-diazabicyclo[2.2.1]heptane-2-(carbonyl)-3-(3-cyclopentyloxy-4-
349 methoxy-phenyl)-4,5-dihydro-isoxozol-5-yl]-5-benzyl-2,5-diazabicyclo-[2.2.1]hept-2-yl-
350 ethanone (Compound No. 175),

WO 2007/045980

PCT/IB2006/002931

- 120 -

- 351 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-piperdin-
352 1-yl-methanone (Compound No. 176),
- 353 4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-
354 piperazine-1-carboxylic acid tert-butyl ester (Compound No. 177),
- 355 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-carbonyl]-
356 pyrrolidin-2-carboxylic acid (Compound No. 178),
- 357 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-carbonyl]-
358 pyrrolidine-2-carboxylic acid methyl ester (Compound No. 179),
- 359 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-yl]-
360 pyrrolidin-1-yl-methanone (Compound No. 180),
- 361 [1-4]-Bipiperidinyl-1-yl-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-
362 isoxazol-5-yl]-methanone (Compound No. 181),
- 363 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-
364 4-phenyl-piperidine-4-yl}-ethanone (Compound No. 182),
- 365 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-
366 methyl-piperazin-1-yl)-methanone (Compound No. 183),
- 367 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]- piperazin-
368 1-yl-methanone (Compound No. 184),
- 369 [4-(4-Chloro-phenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-
370 phenyl)-5-methyl-4,5- dihydroisoxazol-5-yl]-methanone (Compound No. 185),
- 371 {4-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-
372 carbonyl]-[1,4]diazepan-1-yl}-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-
373 dihydro-isoxazol-5-yl]-methanone (Compound No. 186),
- 374 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-
375 cyclopropylmethyl-piperazin-1-yl)-methanone (Compound No. 187),
- 376 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(4-
377 isobutyl-1-piperazin-1-yl)-methanone (Compound No. 188),
- 378 [3-Hydroxymethyl-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-
379 4,5-dihydro-isoxazol-5-yl]-methanone (Compound No. 189),

WO 2007/045980

PCT/IB2006/002931

- 121 -

- 380 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4, 5-dihydro-isoxazol-5-yl]-(4-
381 hydroxy-piperidin-1-yl)-methanone (Compound No. 190),
- 382 (4-Benzyl-piperidin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4, 5-
383 dihydro-isoxazol-5-yl]-methanone (Compound No. 191),
- 384 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4, 5-dihydro-isoxazole-5-carbonyl]-
385 piperidin-4-one (Compound No. 192),
- 386 [4-(4-Bromophenyl)-4-hydroxy-piperidin-1-yl]-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-
387 5-methyl-4, 5-dihydro-isoxazol-5-yl]-methanone (Compound No. 193),
- 388 (5-Benzyl-2, 5-diaza-bicyclo [2.2.1] hept-2-yl- [3-(3-cyclopentyloxy-4-methoxy-phenyl)-
389 5-methyl-4, 5-dihydro-isoxazol-5-yl]-methanone (Compound No. 194),
- 390 (4-Benzyl-piperazin-1-yl)-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4, 5-
391 dihydro-isoxazol-5-yl]-methanone (Compound No. 195),
- 392 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4, 5-dihydro-isoxazole-5-carbonyl]-
393 pyrrolidin-2-carboxylic acid methyl amide (Compound No. 196),
- 394 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-
395 pyrrolidine-2-carboxylic acid diethyl amide (Compound No. 197),
- 396 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl]-(2-
397 hydroxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 198),
- 398 1-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydroisoxazole-5-carbonyl]-
399 piperidine-2-carboxylic acid methyl ester (Compound No. 199),
- 400 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carboxyl]-
401 pyrrolidine-2-carboxylic acid amide (Compound No. 200),
- 402 3-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazole-5-carbonyl]-
403 bicyclo[2.2.1]heptan-2-one (Compound No. 201),
- 404 3-[3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxa-2-aza-spiro[4.4]non-2-en-6-one
405 (Compound No. 202),
- 406 3-[3-Cyclopentyloxy-4-methoxy-phenyl)-7-methyl-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-
407 6,9-dione (Compound No. 203),

WO 2007/045980

PCT/IB2006/002931

- 122 -

- 408 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-methyl-4,5-dihydro-isoxazol-5-yl-(2-
409 methoxymethyl-pyrrolidin-1-yl)-methanone (Compound No. 204),
410 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
411 (Compound No. 205),
412 3-(3-Cyclopropylmethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
413 (Compound No. 206),
414 3-(4-Difluoromethoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
415 (Compound No. 207),
416 3-(4-Difluoro-3-butoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No.
417 208),
418 3-(4-Difluoromethoxy-3-isobutoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
419 (Compound No. 209),
420 3-(3-Cyclopropylmethoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-
421 ene (Compound No. 210),
422 3-(3-Benzyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
423 (Compound No. 211),
424 3-(4-Difluoromethoxy-3-cyclopentyloxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
425 (Compound No. 212),
426 3-(3,4-Bis-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No.
427 213),
428 3-(3-Butoxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro [4,4] non-2-ene
429 (Compound No. 214),
430 3-[3-(Bicyclo[2.2.1]hept-2-yloxy)-4-difluoromethoxy-phenyl]-1,7-dioxo-2-aza-
431 spiro[4.4]non-2-ene (Compound No. 215),
432 3-(4-Difluoromethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
433 (Compound No. 216),
434 3-(4-Benzyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No.
435 217),

WO 2007/045980

PCT/IB2006/002931

- 123 -

136 3-(3-Cycloheptyloxy-4-difluoromethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
137 (Compound No. 218),

138 4-(1,7-Dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 219),

139 3-[3-(indan-2-yloxy)-4-methoxy-phenyl]-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
140 (Compound No. 220),

141 3-(4-Ethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
142 No. 221),

143 3-(3-Methoxy-4-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
144 No. 222),

145 3-(4-Isopropoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
146 No. 223),

147 3-(4-Butoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
148 No. 224),

149 3-(4-Cyclopentyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
150 (Compound No. 225),

151 3-(4-(Isobutoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
152 No. 226),

153 3-(4-Cyclohexyloxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
154 (Compound No. 227),

155 3-(4-Cyclopropylmethoxy-3-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
156 (Compound No. 228),

157 3-(3,4-Dimethoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound No. 229),
158 3-(3-Ethoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
159 No. 230),

160 3-(4-Methoxy-3-propoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
161 No. 231),

162 3-(3-Isopropoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
163 No. 232),

WO 2007/045980

PCT/IB2006/002931

- 124 -

- 464 3-(3-Butoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
465 No. 233),
- 466 3-(3-Isobutoxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
467 No. 234),
- 468 3-[4-Methoxy-3-(3-methyl-butoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
469 (Compound No. 235),
- 470 3-(3-Cyclohexyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
471 (Compound No. 236),
- 472 3-(3-Cycloheptyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro [4.4] non-2-ene
473 (Compound No. 237),
- 474 3-[4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-1,7-dioxo-2-aza-spiro[4.4]non-2-ene
475 (Compound No. 238),
- 476 3-(3-Benzoyloxy-4-methoxy-phenyl)-1,7-dioxo-2-aza-spiro[4.4]non-2-ene (Compound
477 No. 239),
- 478 5-(1,7-Dioxo-2-aza-spiro[4.4]non-2-en-3-yl)-2-methoxy-phenol (Compound No. 240),
- 479 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-
480 carboxylic acid isopropyl ester (Compound No. 241),
- 481 Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-
482 spiro[4.5]dec-2-ene (Compound No. 242),
- 483 4-Chloro-N-[3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-
484 ene-8-carbonyl]-benzene sulfonamide (Compound No. 243),
- 485 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2, 8-diaza-spiro [4.5] dec-2-ene-8-
486 carboxylic acid-(2,6-difluoro-phenyl)-amide (Compound No. 244),
- 487 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,8-diaza-spiro[4.5]dec-2-ene-8-
488 carboxylic acid-(2,4-dichloro-phenyl)-amide (Compound No. 245),
- 489 [3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-carbamic
490 acid isopropyl ester (Compound No. 246),
- 491 Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-
492 2-en-8-ylamine (Compound No. 247),

WO 2007/045980

PCT/IB2006/002931

- 125 -

- 493 2-[3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-en-8-yl]-
494 isoindole-1,3-dione (Compound No. 248),
- 495 7-(3-Cyclopentyloxy-4-methoxy-phenyl)-5-oxa-6-aza-spiro[3.4]oct-6-ene (Compound
496 No. 249),
- 497 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2-aza-spiro[4.5]dec-2-ene (Compound
498 No. 250),
- 499 3-(3-Cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-spiro[4.4]non-2-ene-7-
500 carboxylic acid tert-butyl ester (Compound No. 251),
- 501 Hydrochloride salt of 3-(3-cyclopentyloxy-4-methoxy-phenyl)-1-oxa-2,7-diaza-
502 spiro[4.4]non-2-ene (Compound No. 252),
- 503 3-[3- {[(3*S*)-1-Benzylpyrrolidin-3-yl]oxy} -4-(difluoromethoxy)phenyl]-1,7-dioxa-2-
504 azaspiro[4.4]non-2-ene (Compound No. 253),
- 505 3-[2-(Difluoromethoxy)-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]propan-1-ol
506 (Compound No. 254),
- 507 [2-(Difluoromethoxy)-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetonitrile
508 (Compound No. 255),
- 509 4-[(5*S* or 5*R*)-1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound
510 No. 256),
- 511 4-[(5*R* or 5*S*)-1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound
512 No. 257),
- 513 5-[(5*S* or 5*R*)-1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound
514 No. 258),
- 515 (5*S* or 5*R*)-3-(3,4-Dimethoxyphenyl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No.
516 259),
- 517 (5*R* or 5*S*)-3-(3,4-Dimethoxyphenyl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound
518 No. 260),
- 519 2-(Benzyloxy)-4-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl)phenol (Compound No. 261),

WO 2007/045980

PCT/IB2006/002931

- 126 -

- 520 2-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]ethanol
- 521 (Compound No. 262),
- 522 3-[4-(Difluoromethoxy)-3-ethoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene (Compound
- 523 No. 263),
- 524 3-[3-(Cyclohexyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
- 525 (Compound No. 264),
- 526 (5R or 5S)-3-[4-(Difluoromethoxy)-3-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
- 527 ene (Compound No. 265),
- 528 (5S or 5R)-3-[4-(Difluoromethoxy)-3-methoxyphenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
- 529 ene (Compound No. 266),
- 530 Ethyl [2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetate
- 531 (Compound No. 267),
- 532 3-[4-(Difluoromethoxy)-3-(2-morpholin-4-ylethoxy)phenyl]-1,7-dioxo-2-
- 533 azaspiro[4.4]non-2-ene (Compound No. 268),
- 534 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl
- 535 cyclohexanecarboxylate (Compound No. 269),
- 536 5-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]pentanoic
- 537 acid (Compound No. 270),
- 538 3-[3-(2,2,2-Trifluoroethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
- 539 ene (Compound No. 271),
- 540 3-[3-(Cyclopentylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
- 541 ene (Compound No. 272),
- 542 *N*-cyclopropyl-2-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-
- 543 yl)phenoxy]acetamide (Compound No. 273),
- 544 2-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]acetamide
- 545 (Compound No. 274),
- 546 2-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]-*N*-
- 547 methylacetamide (Compound No. 275),

WO 2007/045980

PCT/IB2006/002931

- 127 -

- 548 3-[3-(Cyclopentyloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
549 ene (Compound No. 276),
- 550 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl
551 cyclopropanecarboxylate (Compound No. 277),
- 552 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl morpholine-4-
553 carboxylate (Compound No. 278),
- 554 2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenyl benzoate
555 (Compound No. 279),
- 556 5-[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy] pentanamide
557 (Compound No. 280),
- 558 3-[3-Propoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
559 (Compound No. 281),
- 560 3-[3-Isopropoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
561 (Compound No. 282),
- 562 3-[3-(Cyclopropylmethoxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-
563 azaspiro[4.4]non-2-ene (Compound No. 283),
- 564 3-[3-(2,3-Dihydro-1*H*-inden-2-yloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-
565 azaspiro[4.4]non-2-ene (Compound No. 284),
- 566 5-(1,7-Dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)phenol (Compound
567 No. 285),
- 568 3-[3-Methoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
569 (Compound No. 286),
- 570 3-[3-Ethoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-ene
571 (Compound No. 287),
- 572 3-[3-Butoxy-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
573 ene10019955 (Compound No. 288),
- 574 3-[3-(Cyclohexylmethoxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-
575 azaspiro[4.4]non-2-ene (Compound No. 289),

WO 2007/045980

PCT/IB2006/002931

- 128 -

- 576 3- {[2-(Difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]methyl}
577 benzonitrile (Compound No. 290),
- 578 2-{2-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]ethyl}-
579 1*H*-isoindole-1,3(2*H*)-dione (Compound No. 291),
- 580 3-[3-(Cyclohexyloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
581 ene (Compound No. 292),
- 582 Ethyl [5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)
583 phenoxy]acetate (Compound No. 293),
- 584 3-[3-(Cyclohexylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxo-2-azaspiro[4.4]non-2-
585 ene (Compound No. 294),
- 586 *Tert*-butyl [2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-
587 yl)phenoxy]acetate (Compound No. 295),
- 588 *N*-cyclopropyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)
589 phenoxy]acetamide (Compound No. 296),
- 590 2-(Cyclopentyloxy)-4-[(5*R* or 5*S*)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol
591 (Compound No. 297),
- 592 2-(Cyclopentyloxy)-4-[(5*S* or 5*R*)-1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl]phenol
593 (Compound No. 298),
- 594 *N*-benzyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)
595 phenoxy]acetamide (Compound No. 299),
- 596 *N*-Cyclopentyl-2-[5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)-2-(2,2,2-trifluoroethoxy)
597 phenoxy]acetamide (Compound No. 300),
- 598 *Tert*-butyl 4-[2-(difluoromethoxy)-5-(1,7-dioxo-2-azaspiro[4.4]non-2-en-3-yl)phenoxy]
599 piperidine-1-carboxylate (Compound No. 301),
- 600 Hydrochloride salt of 3-[4-(difluoromethoxy)-3-(piperidin-4-yloxy)phenyl]-1,7-dioxo-2-
601 azaspiro[4.4]non-2-ene (Compound No. 302),
- 602 3-{3-[(1-Acetylpiperidin-4-yl)oxy]-4-(difluoromethoxy)phenyl}-1,7-dioxo-2-azaspiro
603 [4.4]non-2-ene (Compound No. 303),

WO 2007/045980

PCT/IB2006/002931

- 129 -

- 604 Tert-butyl (3S)-3-[2-(difluoromethoxy)-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-
605 yl)phenoxy]pyrrolidine-1-carboxylate (Compound No. 304),
- 606 Tert-butyl (3R)-3-[2-(difluoromethoxy)-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-
607 yl)phenoxy]pyrrolidine-1-carboxylate (Compound No. 305),
- 608 Tert-butyl 3-[2-(difluoromethoxy)-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-
609 yl)phenoxy]piperidine-1-carboxylate (Compound No. 306),
- 610 Tert-butyl (2S)-2-{{2-(difluoromethoxy)-5-(1,7-dioxa-2-azaspiro[4.4]non-2-en-3-
611 yl)phenoxy}methyl}pyrrolidine-1-carboxylate (Compound No. 307),
- 612 (5R or 5S)-3-[3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-
613 azaspiro[4.4]non-2-ene (Compound No. 308),
- 614 (5S or 5R)-3-(3-isopropoxy-4-methoxyphenyl)-1,7-dioxa-2-azaspiro[4.4]non-2-ene
615 (Compound No. 309),
- 616 (5S or 5R)-3-[3-(Cyclopropylmethoxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-
617 2-ene (Compound No. 310),
- 618 2-(Cyclopropylmethoxy)-4-[(5S or 5R)-1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl]phenol
619 (Compound No. 311),
- 620 4-[(5S or 5R)-1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl]-2-isopropoxyphenol (Compound
621 No. 312),
- 622 (5S or 5R)-3-[3-(cyclopentyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-
623 azaspiro[4.4]non-2-ene (Compound No. 313),
- 624 (5S or 5R)-3-[3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-
625 azaspiro[4.4]non-2-ene (Compound No. 314),
- 626 (5S or 5R)-3-[4-(difluoromethoxy)-3-isopropoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-
627 ene (Compound No. 315),
- 628 (5R or 5S)-3-[4-(difluoromethoxy)-3-isopropoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-
629 ene (Compound No. 316),
- 630 2-(Cyclopropylmethoxy)-4-[(5R or 5S)-1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl]phenol
631 (Compound No. 317),

WO 2007/045980

PCT/IB2006/002931

- 130 -

- 632 4-[(5R or 5S)-1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl]-2-isopropoxyphenol (Compound
633 No. 318),
- 634 (5R or 5S)-3-[3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-
635 azaspiro[4.4]non-2-ene (Compound No. 319),
- 636 (5R or 5S)-3-[4-(difluoromethoxy)-3-isopropoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-
637 ene (Compound No. 320),
- 638 Hydrochloride salt of 3-{4-(difluoromethoxy)-3-[(3S)-pyrrolidin-3-yloxy]phenyl}-1,7-
639 dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 321),
- 640 Hydrochloride salt of 3-{4-(difluoromethoxy)-3-[(2S)-pyrrolidin-2-ylmethoxy]phenyl}-
641 1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 322),
- 642 Hydrochloride salt of 3-{4-(difluoromethoxy)-3-[(2R)-pyrrolidin-2-ylmethoxy]phenyl}-
643 1,7-dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 323),
- 644 3-[4-(Difluoromethoxy)-3-{[(2R)-1-propionylpyrrolidin-2-yl]methoxy}phenyl]-1,7-dioxa-
645 2-azaspiro[4.4]non-2-ene (Compound No. 324),
- 646 3-[3-{[(2S)-1-acetylpyrrolidin-2-yl]methoxy}-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-
647 azaspiro[4.4]non-2-ene (Compound No. 325),
- 648 3-[3-{[(3S)-1-benzoylpyrrolidin-3-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-
649 azaspiro[4.4]non-2-ene (Compound No. 326),
- 650 3-[4-(Difluoromethoxy)-3-{[(3S)-1-propionylpyrrolidin-3-yl]oxy}phenyl]-1,7-dioxa-2-
651 azaspiro[4.4]non-2-ene (Compound No. 327),
- 652 (5S or 5R)-3-[3-(Benzyloxy)-4-(difluoromethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-
653 ene (Compound No. 328),
- 654 2-(Benzyloxy)-4-[(5S or 5R)-1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl]phenol (Compound
655 No. 329),
- 656 (5S or 5R)-3-[3-(Benzyloxy)-4-methoxyphenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene
657 (Compound No. 330),
- 658 3-{4-(Difluoromethoxy)-3-[(1-propionylpiperidin-4-yl)oxy]phenyl}-1,7-dioxa-2-
659 azaspiro[4.4]non-2-ene (Compound No. 331),

WO 2007/045980

PCT/IB2006/002931

- 131 -

- 660 3-[4-(Difluoromethoxy)-3-{[1-(4-fluorobenzoyl)piperidin-4-yl]oxy}phenyl]-1,7-dioxa-2-
661 azaspiro[4.4]non-2-ene (Compound No. 332),
- 662 3-[3-{[1-(Cyclopropylcarbonyl)piperidin-4-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-
663 dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 333),
- 664 3-[3-{[1-(Cyclopentylcarbonyl)piperidin-4-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-
665 dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 334),
- 666 3-[4-(Difluoromethoxy)-3-({1-[(trifluoromethyl)sulfonyl]piperidin-4-yl}oxy)phenyl]-1,7-
667 dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 335),
- 668 3-{3-[(1-Acetylpiperidin-3-yl)oxy]-4-(difluoromethoxy)phenyl}-1,7-dioxa-2-
669 azaspiro[4.4]non-2-ene (Compound No. 336),
- 670 3-{4-(Difluoromethoxy)-3-[(1-propionylpiperidin-3-yl)oxy]phenyl}-1,7-dioxa-2-
671 azaspiro[4.4]non-2-ene (Compound No. 337),
- 672 3-[4-(Difluoromethoxy)-3-{[1-(4-fluorobenzoyl)piperidin-3-yl]oxy}phenyl]-1,7-dioxa-2-
673 azaspiro[4.4]non-2-ene (Compound No. 338),
- 674 3-[3-{[1-(Cyclopropylcarbonyl)piperidin-3-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-
675 dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 339),
- 676 3-[3-{[1-(Cyclopentylcarbonyl)piperidin-3-yl]oxy}-4-(difluoromethoxy)phenyl]-1,7-
677 dioxa-2-azaspiro[4.4]non-2-ene (Compound No. 340),
- 678 3-[4-(Difluoromethoxy)-3-{[1-(ethylsulfonyl)piperidin-3-yl]oxy}phenyl]-1,7-dioxa-2-
679 azaspiro[4.4]non-2-ene (Compound No. 341),
- 680 3-[3-(Benzyloxy)-4-(2,2,2-trifluoroethoxy)phenyl]-1,7-dioxa-2-azaspiro[4.4]non-2-ene
681 (Compound No. 342),
- 682 2-(Difluoromethoxy)-5-[(5*S* or 5*R*)-1,7-dioxa-2-azaspiro[4.4]non-2-en-3-yl]phenol
683 (Compound No. 343),
- 684 5-[(5*R* or 5*S*)-1,7-Dioxa-2-azaspiro[4.4]non-2-en-3-yl]-2-methoxyphenol (Compound No.
685 344).

- 1 3. The pharmaceutical composition of claim 1, wherein the one or more
2 muscarinic receptor antagonists (MRA) are selected from tiotropium salts, methantheline,

WO 2007/045980

PCT/IB2006/002931

- 132 -

3 ipratropium, propantheline, dicyclomine, scopolamine telenzepine, benztropine and
4 atropine.

1 4. The pharmaceutical composition of claim 1, wherein the one or more β 2-
2 agonists are selected from albuterol, salbutamol, biltolterol, pirbuterol, levosalbutamol,
3 tulobuterol, terbutaline, bambuterol, metaproterenol, fenoterol, salmeterol, carmoterol,
4 arformoterol, formoterol, or their pharmaceutically acceptable salts or solvates thereof.

1 5. The pharmaceutical composition of claim 1, wherein the one or more
2 corticosteroids are selected from alclometasone, amcinonide, amelometasone,
3 beclometasone, betamethasone, budesonide, ciclesonide, clobetasol, cloticasone,
4 cyclomethasone, deflazacort, deprodone, dexbudesonide, diflorasone, difluprednate,
5 fluticasone, flunisolide, halometasone, halopredone, hydrocortisone, hydrocortisone,
6 methylprednisolone, mometasone, prednicarbate, prednisolone, rimexolone, tixocortol,
7 triamcinolone, ulobetasol, or pharmaceutically acceptable salts or solvates thereof.

1 6. The pharmaceutical composition of claim 1, wherein one or more PDE-IV
2 and one or more muscarinic receptor antagonists (MRA) are present in a ratio from 1:10 to
3 10:1.

1 7. The pharmaceutical composition of claim 1, wherein one or more PDE-IV
2 and one or more β 2-agonist are present in a ratio from 1:10 to 10:1.

1 8. The pharmaceutical composition of claim 1, wherein one or more PDE-IV
2 and one or more p38 MAP Kinase inhibitors are present in a ratio from 1:10 to 10:1.

1 9. The pharmaceutical composition of claim 1, wherein one or more PDE-IV
2 and one or more corticosteroids are present in a ratio from 1:10 to 10:1.

1 10. A method of treating autoimmune, inflammatory or allergic diseases or
2 disorders comprising administering one or more pharmaceutical compositions of claims 1
3 or 7.

1 11. The method of claim 8, wherein the autoimmune, inflammatory or allergic
2 diseases or disorders are selected from respiratory disorder, asthma, chronic bronchitis,
3 chronic obstructive pulmonary disease, whooping cough, eosinophilic granuloma,
4 psoriasis and other benign or malignant proliferative skin diseases, eczema, inflammatory
5 bowel disease, endotoxic shock, anaphylactic shock, laminitis in horses, septic shock,

WO 2007/045980

PCT/IB2006/002931

- 133 -

- 6 ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain,
- 7 inflammatory arthritis, periodontitis, chronic glomerulonephritis, atopic dermatitis,
- 8 urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome,
- 9 transplant rejection, rhinitis, pruritus, diabetes insipidus, eye diseases, allergic rhinitis,
- 10 allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, atherosclerosis,
- 11 atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, osteoporosis,
- 12 osteoarthritis, inflammation, ankylosing spondylitis, transplant rejection, graft versus host
- 13 disease, hypersecretion of gastric acid, bacterial, fungal induced sepsis, viral induced
- 14 sepsis, fungal induced septic shock, viral induced septic shock, inflammation-mediated
- 15 chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis,
- 16 cancer, cachexia, muscle wasting, depression memory impairment, tumor growth,
- 17 cancerous invasion of normal tissues Hashimoto's thyroiditis (underactive thyroid),
- 18 Graves' disease (overactive thyroid), Lupus and acquired immuno deficiency syndrome.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/002931

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/41 A61P11/00 A61P29/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/030939 A (GLAXO GROUP LTD [GB]; RAPEPORT WILLIAM GARTH [GB]) 17 April 2003 (2003-04-17) claims 1,8	1-11
Y	WO 03/068234 A (PFIZER LTD [GB]; MAGEE THOMAS VICTOR [US]; PFIZER [US]) 21 August 2003 (2003-08-21) claims 7,10-14	1-11
Y	WO 01/32127 A2 (SMITHKLINE BEECHAM CORP [US]; GOODFELLOW PETER N [GB]; NIEMAN RICHARD) 10 May 2001 (2001-05-10) claim 1	1-11
	----- -/--	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the International search

31 January 2007

Date of mailing of the International search report

22/02/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Renard, Delphine

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/002931

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/096463 A (PFIZER [US]; YEADON MICHAEL [GB]; WATSON JOHN W [US]; ARMSTRONG ROISIN) 5 December 2002 (2002-12-05) claims 1,11,12 -----	1-11
Y	WO 2005/009966 A (PFIZER LTD [GB]; BAILEY SIMON [US]; BARBER CHRISTOPHER GORDON [GB]; GL) 3 February 2005 (2005-02-03) claim 20 -----	1-9
Y	ODINGO J O: "Inhibitors of PDE4: A review of recent patent literature" EXPERT OPINION ON THERAPEUTIC PATENTS 2005 UNITED KINGDOM, vol. 15, no. 7, 2005, pages 773-787, XP002413778 ISSN: 1354-3776 page 782 - page 783 -----	1-11
Y	WO 2005/021515 A2 (RANBAXY LAB LTD [IN]; PALLE VENKATA P [IN]; BALACHANDRAN SARALA [IN];) 10 March 2005 (2005-03-10) claims 1,11,13,14 -----	1-11
Y	US 5 686 434 A (KLEINMAN EDWARD FOX [US]) 11 November 1997 (1997-11-11) claims 1,13,14 -----	1-11
P,Y	WO 2006/085212 A2 (RANBAXY LAB LTD [IN]; PALLE VENKATA P [IN]; BALACHANDRAN SARALA [IN];) 17 August 2006 (2006-08-17) claims 1-4 -----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/002931

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03030939	A	17-04-2003	EP 1438071 A1	21-07-2004
			JP 2005507905 T	24-03-2005
			US 2005070514 A1	31-03-2005
WO 03068234	A	21-08-2003	AU 2003202116 A1	04-09-2003
			AU 2003245812 A1	04-09-2003
			BR 0307574 A	21-12-2004
			CA 2475708 A1	21-08-2003
			EP 1476157 A1	17-11-2004
			WO 03068232 A1	21-08-2003
			JP 2005522449 T	28-07-2005
			MX PA04007736 A	15-10-2004
WO 0132127	A2	10-05-2001	AR 029189 A1	18-06-2003
			AU 1357501 A	14-05-2001
			BG 106748 A	28-02-2003
			BR 0015270 A	18-06-2002
			CA 2388333 A1	10-05-2001
			CN 1387404 A	25-12-2002
			CZ 20021512 A3	16-04-2003
			EP 1225866 A2	31-07-2002
			HU 0203152 A2	28-01-2003
			JP 2003513028 T	08-04-2003
			MA 26841 A1	20-12-2004
			MX PA02004350 A	07-11-2002
			NO 20022057 A	27-06-2002
			OA 12076 A	04-05-2006
			PL 355261 A1	05-04-2004
			SK 7592002 A3	06-11-2002
			TR 200201211 T2	21-08-2002
			TW 242431 B	01-11-2005
			ZA 200203435 A	30-04-2003
WO 02096463	A	05-12-2002	BG 108382 A	30-12-2004
			BR 0209992 A	06-04-2004
			CA 2446613 A1	05-12-2002
			CN 1511042 A	07-07-2004
			CZ 20033150 A3	16-06-2004
			EE 200300585 A	15-04-2004
			EP 1395288 A1	10-03-2004
			HU 0400037 A2	28-04-2004
			JP 2005508861 T	07-04-2005
			MA 27027 A1	20-12-2004
			MX PA03010162 A	10-03-2004
			NZ 529335 A	30-09-2005
			OA 12610 A	09-06-2006
			PL 367085 A1	21-02-2005
			SK 14312003 A3	03-08-2004
			US 2004147544 A1	29-07-2004
WO 2005009966	A	03-02-2005	BR PI0412903 A	26-09-2006
			CA 2534262 A1	03-02-2005
			EP 1651609 A1	03-05-2006
			JP 2006528660 T	21-12-2006
			MX PA06001039 A	11-04-2006
WO 2005021515	A2	10-03-2005	AU 2004268847 A1	10-03-2005
			BR PI0413330 A	10-10-2006

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2006/002931

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005021515	A2	CA 2537185 A1 EP 1663999 A2	10-03-2005 07-06-2006
US 5686434	A	11-11-1997	AT 187447 T 15-12-1999 CA 2177375 A1 01-06-1995 DE 69422061 D1 13-01-2000 DE 69422061 T2 30-03-2000 DK 730587 T3 10-04-2000 EP 0730587 A1 11-09-1996 ES 2139754 T3 16-02-2000 FI 945556 A 27-05-1995 GR 3032506 T3 31-05-2000 WO 9514680 A1 01-06-1995 JP 2818820 B2 30-10-1998 JP 9500146 T 07-01-1997 PT 730587 T 31-05-2000
WO 2006085212	A2	17-08-2006	NONE